Diagnostic and Interventional Imaging (2019) **100**, 391—400

SOLICITATED REVIEW /*Interventional imaging*

Interventional radiology techniques for pain reduction and mobility improvement in patients with knee osteoarthritis

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KEYWORDS
Knee;
Osteoarthritis;
Pain;
Intra-articular injections;
Interventional radiology

Abstract Osteoarthritis of the knee is the most common cause of chronic knee pain being more prevalent in middle-aged and elderly patients. Symptomatic patients complain of pain and mobility impairment. Therapeutic armamentarium includes physical therapy, oral pharmacologic therapy, intra-articular injections, nerve ablation or modulation, trans-catheter arterial embolization, minimally invasive arthroscopic treatment and partial or total knee arthroplasty. Interventional radiology therapies for knee osteoarthritis include intra-articular injections, neurotomy and neuromodulation techniques as well as transcatheter intra-arterial therapies. These therapies aim to control pain and inflammation, improve mobility and function whilst the novel cell-based therapies have the potential for bone and cartilage regenerative repair facilitating the delay to surgery. The purpose of this review is to illustrate the technical aspects, the indications and the methodology of local therapies for knee osteoarthritis performed by interventional radiologists and provide current evidence.

Osteoarthritis of the knee is the most common cause of chronic knee pain and represents a major cause of disability and burden on healthcare systems worldwide, being more prevalent in middle-aged and elderly patients [1]. Knee osteoarthritis is characterized by progressive degradation of articular cartilage and bone remodeling whilst risk factors for knee include increased age, obesity and mechanical stress or trauma to the joint [2]. Although most of patients with knee osteoarthritis present with a discrepancy between clinical and imaging findings, x-rays and magnetic resonance imaging are currently the most commonly applied modalities for diagnosis, prognosis and therapeutic efficacy [3—5]. Depending on the severity of knee osteoarthritis, various treatments can be used, including physical therapy,

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https://doi.org/10.1016/j.diii.2019.02.011

oral pharmacologic therapy, intra-articular injections, nerve ablation or modulation, trans-catheter arterial embolization, minimally invasive arthroscopic treatment and partial or total knee arthroplasty [6—12]. However, no single treatment has proven complete effectiveness.

Local therapies for knee osteoarthritis comprise intra-articular injections, neurotomy and neuromodulation techniques as well as transcatheter intra-arterial therapies. These therapies aim at controlling pain and inflammation, improve mobility and function whilst the novel cell-based therapies have the potential for bone and cartilage regenerative repair facilitating the delay to surgery which is offered when conservative and local minimally invasive treatments no longer control patient's pain.

The purpose of this review is to illustrate the technical aspects, the indications and the methodology of all local therapies for knee osteoarthritis performed by interventional radiologists and provide current evidence.

Intra-articular injections

Intra-articular corticosteroids

Intra-articular corticosteroids are recommended by treatment guidelines and widely used in knee osteoarthritis. However, no consensus exists regarding their safety and efficacy [12—16]. Corticosteroids have anti-inflammatory and immunosuppressive effects as they directly act on nuclear steroid receptors and interrupt the inflammatory-immune cascade [17]. These agents reduce cytokine diapedesis within the capillary endothelium, inhibit inflammatory cell accumulation, adhesion, phagocytosis and immunoglobulin synthesis as well as the release of prostaglandin and leukotriene [18—20].

Corticosteroids used for the treatment of knee osteoarthritis include triamcinolone acetonide, methylprednisolone acetate, betamethasone acetate, betamethasone sodium phosphate, and dexamethasone sodium phosphate [21,22]. The selection of the specific drug varies according to physician's preference. However, when compared to other corticosteroids, triamcinolone acetonide has greater potential, longer duration of action and rare flare reaction [22].

Corticosteroids provide short-term moderate pain relief for up to 3—4 weeks post intra-articular knee injection; extended-release formulations have been designed to provide prolonged analgesia with a similar to saline placebo safety profile [23—25]. The response to this kind of intra-articular injection is suggested to be better in less severe radiographic stages or in the presence of a joint effusion; specifically in the latter case, the response regarding pain or ultrasound synovial effusion at one month after corticosteroid injection is suggested to predict the response at one year [26—28]. Patients should be advised that the analgesic effects of intra-articular corticosteroid injections are time-limited as these injections are not suggested to provide sustained symptom relief for over 2 years of follow-up [29].

Intra-articular corticosteroid injections, especially when repeated, can be related to rare adverse effects comprising joint infection, tendinopathy, local nerve damage, skin atrophy, osteoporosis, increased cartilage loss and hyperglycemia while acute complications of the technique are rare [30—32]. In current practice, the interval between corticosteroid injections is recommended to be between 2—6 weeks and it is advised not to perform more than 3—4 injections per year [33].

Hyaluronic acid derivatives injection

Hyaluronic acid (HA) is a glycosaminoglycan molecule and a natural major component of synovial fluid and it is also present in hyaline cartilage [13,34,35]. The amount of HA approximates 3—4 ml in each knee and acts as a joint lubricant and shock absorber, improving joint elasticity and viscosity, and also it provides nutrients to the cartilage. It is secreted by type B synoviocytes of the joint capsule [36]. In knee osteoarthritis HA undergoes degradation and its molecular weight and concentration is reduced, correlating with pain and functional impairment and increasing the susceptibility of joint cartilage to degenerate [37—39].

Viscosupplementation with HA derivatives has been widely used to treat pain in knee osteoarthritis and HA is the most commonly used injectable drug aside from corticosteroids [40,41]. The primary mechanism of action is the restoration of the lubrication of the joint but although the residence time of HA inside the joint approximates 2—3 days, the effects are sustained for several weeks after HA injection suggesting the presence of additional mechanisms of action which possibly have disease-modifying effects [42]. HA may have immunosuppressive and anti-inflammatory effects whilst viscosupplementation stimulates chondrocyte production of hyaluronate and prevents chondrocyte degradation [43]. Although there are numerous HA derivatives marketed nowadays differing on the basis of origin (from avian or synthetic), reticulation (linear or reticulated), chain length (low or high molecular weight), sterilization process (heat or ultra-filtration), dosing (single or multiple injections and presence or not of associated adjuvants (mannitol, sorbitol,chondroitin sulfate) the major classification is into low molecular weight linear and high molecular weight reticulated products [44]. Reticulated HA derivatives are 3-dimensional structure of linked HA chains which are administrated as a single dose in most of the cases offering slower degradation and longer joint residence [44].

For HA injection, the lateral mid- and supero-lateral patelar approaches are strongly recommended whilst imaging guidance verifies correct intra-articular needle location especially in obese patients or in the case of severe patellofemoral osteoarthritis (Fig. 1). Most common modalities for imaging guidance include ultrasonography or fluoroscopy [11].

Intra-articular injection of HA (especially agents of high molecular weight) is widely used and recommended in the management of patients with knee osteoarthritis with mild to moderate clinically and radiologically confirmed disease who either had not received other therapies or in whom non-pharmacologic or pharmacologic therapies had failed or had a limited response [45—47]. Complications associated with intra-articular HA injection are rare and because of its very good safety profile and favorable benefit/risk ratio it can be used even in elderly or frail patients [11,48].

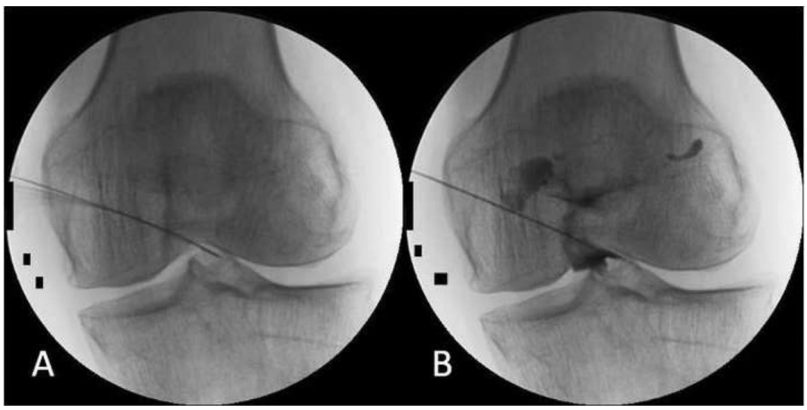

Figure 1. A 57-year-old man with knee osteoarthritis undergoing intra-articular injection under fluoroscopy guidance. A. Fluoroscopy image in antero-posterior projection shows a 22-G needle inserted inside the knee joint using a superior lateral approach. B. After intra articular administration of iodinated contrast material through the 22-G needle, fluoroscopy image confirms correct needle placement inside the knee joint.

Figure 2. Photographs show the different steps for mesenchymal stem cells (MSC) harvesting. A. Under local anesthesia or mild sedation MSC can be harvested from the subumbilical fat. B. The fat sample undergoes centrifugation and MSC are isolated. C. Isolated MSC are aspirated and further injected inside the knee joint (not shown) (courtesy of Dimitrios Tsoukas, MD, Athens, Greece).

The most commonly reported adverse effects of viscosupplementation include injection site reactions such as local pain, swelling and arthralgia which were transient [49]. Sterile synovitis is a rare, painful but typically self-limited disease that is specific to HA injections; it is recommended not to perform viscosupplementation in patients with a history or radiographic evidence of calcium pyrophosphate dihydrate arthropathy [12,50—52]. The overall rate of adverse effects after repeat injection courses is very low [49,53].

Viscosupplementation with HA has a delayed onset of action providing pain relief 2—3 weeks after injection but the effects can last up to 6 months whilst retreatment can be considered in patients with pain recurrence [54,55].

Intra-articular injections are effective in reducing symptoms in short term clinical trials, however, studies on the long-term effects of HA are limited and with inconclusive results regarding sustained symptom relief and delay in need of total knee arthroplasty [29,41,49,56,57]. Combined injections of corticosteroids and HA can provide an increased reduction in pain in the first 2—4 weeks post injection and at 24—26 and 52 weeks as suggested by a Level II meta-analysis [58]. Factors with negative impact on the outcome of viscosupplementation include obesity, a large synovial fluid effusion, a severe joint space narrowing, major malalignment, a severe and/or isolated pattelo-femoral involvement and failure of a previous HA injection [11].

Platelet-rich plasma injection

Platelet-rich plasma (PRP) is a blood derived product, prepared by the centrifugation of autologous whole blood, which has a high concentration of platelets that is generally 4—6 times higher than the subject's baseline platelets concentration [59,60]. PRP is high in growth factors which are stored in platelet α-granules and have been shown to stimulate in vivo HA formation and decrease cartilage metabolism [61,62]. Due to its regenerative and anti-inflammatory effects PRP has been used for intra-articular treatment of mild to moderate knee osteoarthritis with favorable outcomes [59]. When compared to placebo saline injections PRP injections significantly reduce knee pain and improve physical function; when compared to HA or other intra-articular knee injections PRP provide greater clinical improvement at 1 year post-injection and are more efficacious in terms of pain relief and self-imported function improvement [6,59,63,64]. Adverse effects of PRP injection and collection include injection site pain, infection, joint stiffness, bleeding and non-specific symptoms such as syncope, dizziness, headache, nausea, tachycardia and gastritis [65]. At the moment there are no clear guidelines concerning exclusion of intra-articular corticosteroids when PRP is injected, however, as a general practice intra-articular PRP injection should be performed at least 3 weeks post any potential corticosteroid injection.

Mesenchymal stem cell injection

Injection of mesenchymal stem cells (MSC) is an alternative treatment option for osteoarthritic knee pain; these cells secrete, according to the local microenvironment, growth factors, chemokines, cytokine, anti-inflammatory and immunomodulatory molecules and thus, are considered to offer cartilage regeneration or repair [66]. MSCs can be obtained using minimally invasive techniques from bone marrow or adipose tissue (autologous MSC) (Fig. 2) or from amniotic fluid and membrane (allogeneic MSC); in vitro expansion of these cells aims at the selection of a more homogenous MSC population [66—68]. Due to the low immunogenicity allogeneic may be a better alternative than autologous MSCs in old patients or in the case of co-morbidities where these cells can have reduced potential to regenerate [69—72]. The current literature suggests that MSC injections are safe and produce positive clinical outcomes in terms of pain, knee function, quality of life and cartilage volume; these current studies have limited follow-up periods and there is no consensus about the ideal therapeutic dose for MSCs injection in knee osteoarthritis [14,66,73,74]. Adverse events related to MSC treatment are not severe and include knee pain and swelling [14]. Before MSC injection can be used on a wider scale, more research is needed with high-level studies to draw definite conclusions about the efficacy and long-term durability of this treatment [12,14,66,73].

Other injectable treatments

Intraarticular onabotulinum toxin A has been used to reduce osteoarthritic knee pain, however the reported results are inconsistent and conflicting so further trials are necessary to assess its role, if any, as a therapeutic approach for knee osteoarthritis [12,75,76]. Another experimental therapy is intraarticular injection of ozone gas, which showed reduction of pain and improvement of knee function and quality of life in knee osteoarthritis but lasting for a shorter period of time compared to HA and PRP, with adverse events including only puncture-related reports [77,78]. In knee osteoarthritis treatment, a gene therapy approach involving the intraarticular injection of human chondrocytes expressing TGF-β1 (TG-C) has also been used showing improvement in knee pain and function and delayed progression of cartilage damage but further studies are needed to elucidate the long-term therapeutic effects of this approach [79—81].

Neurolysis—Neuromodulation

Both techniques aim to palliative management of chronic pain secondary to knee osteoarthritis (even in the presence of an artificial joint); ablation modalities for neurolysis include radiofrequency (continuous mode) or cryotherapy whilst pulsed radiofrequency mode can be used for neuromodulation [8,82]. The targets for neurolysis include the genicular nerve branches, or peri-articularly targeting pericapsular saphenous nerve branch endings [8,12,82]. Genicular nerves arise from branches of the sciatic, femoral and obturator nerves which are derived from the lumbar plexus [83,84]. The typical targets during neurolysis include the superior lateral, the superior medial and inferior medial genicular nerves running at the femoral or tibial epicondyles level respectively (Fig. 3) [82,85,86]. Bony landmarks and imaging guidance are pre-requisites for safe and correct needle placement in extra-articular neurolysis. Prior to the ablation session the physician must perform stimulation tests to the target area and confirm sensory as evidenced by the presence of nerve related pain, in the absence of any motor nerve response [12]. Extra-articular neuromodulation can be performed with pulsed radiofrequency mode in the same target locations [8,86—88]. With both techniques, adverse events are rare and the only worrisome theoretical complication is vascular injury of the geniculate arteries that can result in pseudoaneurysm or arteriovenous fistula formation, hemarthrosis or osteonecrosis [89]. Pulsed radiofrequency ablation (RFA) tends to have much less, if any, effects but the procedure is less painful with a smaller risk for development of deafferentation pain compared to conventional RFA [87,90]. Current evidence suggests that RFA can be a safe and technically successful neuromodulation technique, with pain reduction in knee lasting between 3 and 12 months after the procedure. The use of RFA is suggested in patients with confirmed nerve-related pain but further research is required to better assess relative effectiveness compared to other treatments [8,12,87,88]. In a similar way, percutaneous cryotherapy with the direct application of low temperatures (—20 to—100 °C) in nerve endings causes Wallerian degeneration and disrupts nerve conduction with additional reduction in blood flow and anti-inflammatory effects on the target area [91—94]. Percutaneous cryoneurolysis had been used for the treatment of knee osteoarthritis pain with favorable results compared to sham treatment for up to 150 days with no occurrence of serious complications [95].

Table 1 Interventional radiology techniques for pain reduction and mobility improvement in knee osteoarthritis.

Technique	Practical aspect	Level of evidence	Included in guidelines
Intra-articular corticosteroids	Standard intra-articular approach	Conditionally to fully recommended	Yes
Intra-articular hyaluronic acid derivatives	Standard intra-articular approach	Conditionally to fully recommended	Yes
Intra-articular plasma rich proteins	Standard intra-articular approach—vein puncture for blood sampling and centrifugation	No recommendations	No
Intra-articular stem cells	Standard intra-articular approach—abdominal fat puncture for sampling	No recommendations	No
Percutaneous neurolysis	3 RFA needles are placed extra-articularly	No recommendations	No
Percutaneous neuromodulation	Standard intra-articular approach with a single RFA needle	No recommendations	No
Trans-arterial embolization	Standard embolization technique of genocular arteries	No recommendations	No

RFA indicates radiofrequency ablation

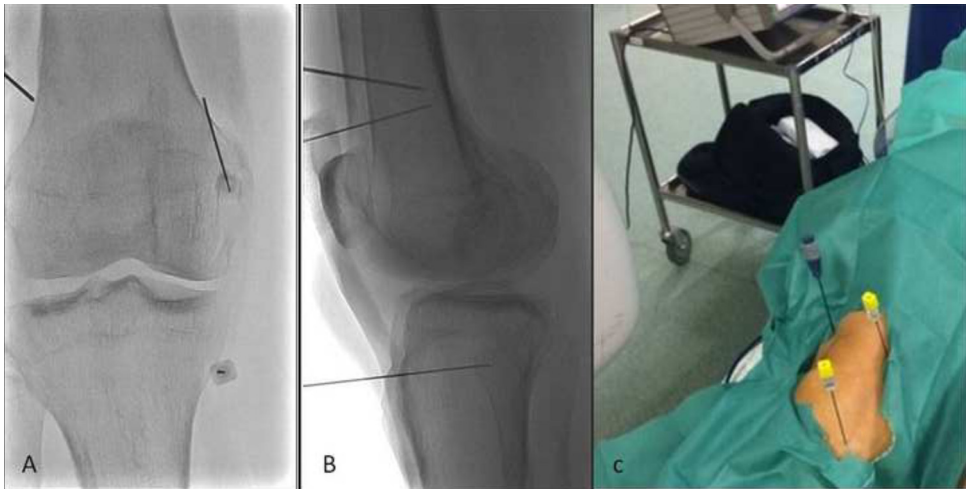

Figure 3. A 54-year-old woman with knee osteoarthritis undergoing fluoroscopy-guided neurolysis of genicular nerves. A. Fluorocopy image in antero-posterior projection shows the three radiofrequency electrodes that have been placed at the level of the superior lateral, superior medial and inferior medial genicular nerves running at the femoral or tibial epicondyles level respectively. B. Fluoroscopy image in right to left projection (lateral view) shows final position of the three electrodes. The three electrodes are correctly placed at the junction of posterior and middle thirds of the bone. C. Photograph shows the three radiofrequency electrodes that have been placed. Sensory and motor stimulation tests will follow before neurolysis session.

Percutaneous neuromodulation can also be performed through an intra-articular approach with the RFA trocar inserted from the antero-lateral region of the knee joint (Fig. 4). With the pulsed mode neurolysis the long silent phases (480 msec) between the short bursts of energy application (10—20 msec) maintain tissue temperature below the irreversible tissue damage threshold (the long silent phases (480 msec) between the short bursts of energy application (10—20 msec) maintain tissue temperature below the irreversible tissue damage threshold

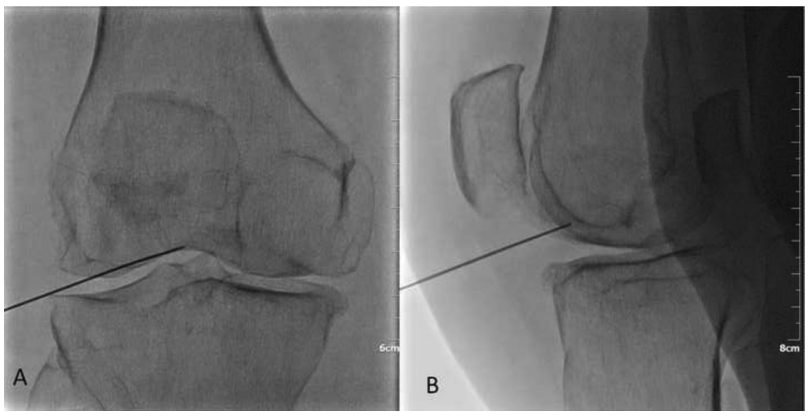

Figure 4. A 82-year-old woman with knee osteoarthritis undergoing fluoroscopy guided intra-articular neuromodulation. A. Fluorocopy image in antero-posterior projection shows radiofrequency electrode inserted from the antero-lateral region of the knee joint. B. Fluoroscopy image in right to left projection (lateral view) shows the final position of the radiofrequency trocar inside the knee joint. The two views confirm that the tip of the trocar is correctly placed (midline and in an equidistant level between tibial and femoral bones).

[8]. Intra-articular pulsed RF neurolysis is reported to suppress the excitatory C fiber response and the synaptic transmission resulting in immediate pain relief; additionally, it causes an immune response interrupting production of pro-inflammatory cytokines, such as interleukin-1b and interleukin-6[8].

Trans-catheter arterial embolization

Trans-catheter arterial embolization of geniculate arteries is a novel minimal invasive technique that has been used to alleviate pain in knee osteoarthritis and is based on the observation that inflammation causes abnormal neovascularization and accompanying sensory nerves to grow, thus the decrease of abnormal blood flow in the periarticular soft tissues via embolization is a means for suppression of inflammation and reduction of pain [96,97].

Transcatheter arterial embolization of geniculate arteries has been used in patients with resistant to conservative management mild to moderate radiographic knee osteoarthritis resulting in improvement of pain scores and knee function that were maintained for 4—19 months or as long as 4 years of follow-up without serious adverse effects [96,97]. Technical success of embolization, which was performed with temporary embolic materials, was 100% and cumulative clinical success rate at 6 months was 86.3% and at 3 years was 79.8% [96,97]. Adverse events that were related to embolization were minor, including subcutaneous hemorrhage at the puncture site and transient cutaneous color change on the treated knee that resolved without treatment [97]. Non-target embolization can lead to potential bone infarction or transient numbness [12].

Evaluating osteoarthritis local therapies

To date, only intra-articular injections of hyaluronic acid derivatives or corticosteroids are included in the proposed therapeutic algorithm by a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) (Table 1) [98]. There is a clear need for improving level of evidence for the rest of the techniques described in this review. The economic burden of osteoarthritis is significant including both direct (hospital admissions, medical examinations, drug therapy) as well as indirect (e.g., losses in productivity resulting from absence from work) costs. All the proposed therapies including total joint replacement aim in pain reduction and mobility improvement targeting in higher life quality. At the moment and although the treatment costs (mostly due to surgical therapies) steadily increase there are no studies allowing ready comparisons between different techniques and therefore it is hard for solid conclusions to be drawn esp concerning cost effectiveness. Another significant disadvantage for cost effectiveness evaluation is the wide variety of products and prices available throughout the globe rendering any comparison extremely difficult.

Conclusion

Osteoarthritis of the knee joint is a common condition that constitutes a significant burden on global healthcare; in the management of osteoarthritic symptoms many different local interventions have been used to relieve pain, improve knee function and prolong the time to arthroplasty. Local therapies comprise intra-articular injections, neurotomy and neuromodulation techniques and transcatheter intra-arterial therapies which, in comparison to knee arthroplasty are less expensive and need a shorter hospital stay; these techniques have been proven safe and efficient in improving knee osteoarthritis symptoms. Local therapies for knee osteoarthritis are governed by inconsistent and controversial evidence; intra-articular injections of corticosteroids and hyaluronic acid derivatives are conditionally to fully recommended whilst there are no recommendations for the rest of the local therapies [97]. At present intra-articular injections of corticosteroids, hyaluronic acid derivatives and PRP as well as genicular nerve neurolysis are included to the routine knee osteoarthritis therapies. Intra-articular stem cells injection, neuromodulation and trans-arterial embolization have just started gaining acceptance whilst further trials are necessary to assess the role of ozone, onabotulinumtoxin A and human chondrocytes. The treatment approach should

be personalized and patient-centered to achieve successful clinical outcomes. Further research is required to investigate the potential of minimal invasive techniques to affect or reverse the progression of the chronic destructive disease process.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

Funding

This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for authorship.

CRediT authorship contribution statement

Dimitrios Filippiadis, George Charalampopoulos, Argyro Mazioti, Efthymia Alexopoulou, Thomas Vrachliotis, Elias Brountzos, Nikolaos Kelekis, Alexis Kelekis.

Substantial contribution to the study conception and design, data acquisition, analysis, and interpretation.

Drafting or revising the article for intellectual content.

Agreement to be accountable for all aspects of the work related to the accuracy or integrity of any part of the work.

Approval of the final version.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Garstang SV, Stitik TP. Osteoarthritis: epidemiology, risk factors, and pathophysiology. Am J Phys Med Rehabil 2006;85:S2—11.
[2] Hunter DJ, Guermazi A. Imaging techniques in osteoarthritis. PM R 2012;4:S68—74.
[3] Boesen M, Ellegaard K, Henriksen M, Gudbergsen H, Hansen P, Bliddal H, et al. Osteoarthritis year in review 2016: Imaging. Osteoarthritis Cartilage 2017;25:216—26.
[4] Unlu EN, Turhan Y, Kos DM, Safak AA. Assessment of anterior subcutaneous hypersignal on proton-density-weighted MR imaging of the knee and relationship with anterior knee pain. Diagn Interv Imaging 2017;98:339—45.
[5] Mourad C, Laperre K, Halut M, Galant C, Van Cauter M, Vande Berg BC. Fused micro-computed tomography (μCT) and histological images of bone specimens. Diagn Interv Imaging 2018;99:501—5.
[6] Dai WL, Zhou AG, Zhang H, Zhang J. Efficacy of platelet-rich plasma in the treatment of knee osteoarthritis: a meta-analysis of randomized controlled trials. Arthroscopy 2017;33:659—70 [e1].
[7] de Rooij M, van der Leeden M, Cheung J, van der Esch M, Hakkinen A, Haverkamp D, et al. Efficacy of tailored exercise therapy on physical functioning in patients with knee osteoarthritis and comorbidity: a randomized controlled trial. Arthritis Care Res 2017;69:807—16.
[8] Filippiadis D, Velonakis G, Mazioti A, Konstantos C, Brountzos E, Kelekis N, et al. Intra-articular application of pulsed radiofrequency combined with viscosupplementation for improvement of knee osteoarthritis symptoms: a single centre prospective study. Int J Hyperthermia 2018;34:1265—9.
[9] Skou ST, Roos EM, Simonsen O, Laursen MB, Rathleff MS, Arendt-Nielsen L, et al. The efficacy of non-surgical treatment on pain and sensitization in patients with knee osteoarthritis: a pre-defined ancillary analysis from a randomized controlled trial. Osteoarthritis Cartilage 2016;24:108—16.
[10] Smith NA, Parsons N, Wright D, Hutchinson C, Metcalfe A, Thompson P, et al. A pilot randomized trial of meniscal allograft transplantation versus personalized physiotherapy for patients with a symptomatic meniscal deficient knee compartment. Bone Joint J 2018;100:56—63.
[11] Conrozier T, Monfort J, Chevalier X, Raman R, Richette P, Diracoglu D, et al. EUROVISCO Recommendations for optimizing the clinical results of viscosupplementation in osteoarthritis. CART 2018 [1947603518783455].
[12] Goldman DT, Piechowiak R, Nissman D, Bagla S, Isaacson A. Current concepts and future directions of minimally invasive treatment for knee pain. Curr Rheumatol Rep 2018;20:54.
[13] Bert JM, Bert TM. Nonoperative treatment of unicompartmental arthritis: from bracing to injection. Clin Sports Med 2014;33:1—10.
[14] Iijima H, Isho T, Kuroki H, Takahashi M, Aoyama T. Effectiveness of mesenchymal stem cells for treating patients with knee osteoarthritis: a meta-analysis toward the establishment of effective regenerative rehabilitation. NPJ Regen Med 2018;3:15.
[15] McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22:363—88.
[16] Miller JH, White J, Norton TH. The value of intra-articular injections in osteoarthritis of the knee. J Bone Joint Surg Br 1958;40:636—43.
[17] Bisicchia S, Tudisco C. Hyaluronic acid vs corticosteroids in symptomatic knee osteoarthritis: a mini-review of the literature. Clin Cases Miner Bone Metab 2017;14:182—5.
[18] Caldwell JR. Intra-articular corticosteroids: guide to selection and indications for use. Drugs 1996;52:507—14.
[19] Ostergaard M, Halberg P. Intra-articular corticosteroids in arthritic disease: a guide to treatment. Bio Drugs 1998;9:95—103.
[20] Creamer P. Intra-articular corticosteroid treatment in osteoarthritis. Curr Opin Rheumatol 1999;11:417—21.
[21] Douglas RJ. Corticosteroid injection into the osteoarthritic knee: drug selection, dose, and injection frequency. Int J Clin Pract 2012;66:699—704.

[22] Vaishya R, Pandit R, Agarwal AK, Vijay V. Intra-articular hyaluronic acid is superior to steroids in knee osteoarthritis: A comparative, randomized study. J Clin Orthop Trauma 2017;8:85—8.
[23] Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006:Cd005328.
[24] da Costa BR, Hari R, Juni P. Intra-articular corticosteroids for osteoarthritis of the knee. JAMA 2016;316:2671—2.
[25] Conaghan PG, Cohen SB, Berenbaum F, Lufkin J, Johnson JR, Bodick N. Brief report: a phase IIb trial of a novel extended-release microsphere formulation of triamcinolone acetonide for intraarticular injection in knee osteoarthritis. Arthritis Care Res 2018;70:204—11.
[26] Arden NK, Reading IC, Jordan KM, Thomas L, Platten H, Hassan A, et al. A randomised controlled trial of tidal irrigation vs corticosteroid injection in knee osteoarthritis: the KIVIS Study. Osteoarthritis Cartilage 2008;16:733—9.
[27] Gaffney K, Ledingham J, Perry JD. Intra-articular triamcinolone hexacetonide in knee osteoarthritis: factors influencing the clinical response. Ann Rheum Dis 1995;54:379—81.
[28] Calvet J, Orellana C, Galisteo C, Garcia-Manrique M, Navarro N, Caixas A, et al. Clinical and ultrasonographic features associated to response to intraarticular corticosteroid injection: a one year follow up prospective cohort study in knee osteoarthritis patient with joint effusion. PloS One 2018;13:e0191342.
[29] Liu SH, Dube CE, Eaton CB, Driban JB, McAlindon TE, Lapane KL. Longterm effectiveness of intraarticular injections on patient-reported symptoms in knee osteoarthritis. J Rheumatol 2018;45:1316—24.
[30] 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;317:1967—75.
[31] Nguyen C, Rannou F. The safety of intra-articular injections for the treatment of knee osteoarthritis: a critical narrative review. Expert Opin Drug Saf 2017;16:897—902.
[32] Uni P, Hari R, Rutjes AW, Fischer R, Silletta MG, Reichenbach S, et al. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database Syst Rev 2015:Cd005328.
[33] Kumar A, Dhir V, Sharma S, Sharma A, Singh S. Efficacy of methylprednisolone acetate versus triamcinolone acetonide intra-articular knee injection in patients with chronicinflammatory aathritis: a 24-week randomized controlled trial. Clin Ther 2017;39:150—8.
[34] 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 Rheumatol 1967;10:357—76.
[35] Gibbs DA, Merrill EW, Smith KA, Balazs EA. Rheology of hyaluronic acid. Biopolymers 1968;6:777—91.
[36] Fraser JR, Laurent TC, Laurent UB, Hyaluronan:. its nature, distribution, functions and turnover. J Intern Med 1997;242:27—33.
[37] Dahl LB, Dahl IM, Engstrom-Laurent A, Granath K. Concentration and molecular weight of sodium hyaluronate in synovial fluid from patients with rheumatoid arthritis and other arthropathies. Ann Rheum Dis 1985;44:817—22.
[38] 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.
[39] Band PA, Heeter J, Wisniewski HG, Liublinska V, Pattanayak CW, Karia RJ, et al. Hyaluronan molecular weight distribution is associated with the risk of knee osteoarthritis progression. Osteoarthritis Cartilage 2015;23:70—6.
[40] Richards MM, Maxwell JS, Weng L, Angelos MG, Golzarian J. Intra-articular treatment of knee osteoarthritis: from anti-inflammatories to products of regenerative medicine. Phys Sportsmed 2016;44:101—8.
[41] Delbarre A, Amor B, Bardoulat I, Tetafort A, Pelletier-Fleury N. Do intra-articular hyaluronic acid injections delay total knee replacement in patients with osteoarthritis: a Cox model analysis. PloS One 2017;12:e0187227.
[42] Fakhari A, Berkland C. Applications and emerging trends of hyaluronic acid in tissue engineering, as a dermal filler and in osteoarthritis treatment. Acta Biomater 2013;9:7081—92.
[43] Moreland LW. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. Arthritis Res Ther 2003;5:54—67.
[44] Legré-Boyer V, Viscosupplementation:. techniques, indications, results. Orthop Traumatol Surg Res 2015;101:S101—8.
[45] Bhandari M, Bannuru RR, Babins EM, Martel-Pelletier J, Khan M, Raynauld JP, et al. Intra-articular hyaluronic acid in the treatment of knee osteoarthritis: a Canadian evidence-based perspective. Ther Adv Musculoskelet Dis 2017;9:231—46.
[46] Cooper C, Rannou F, Richette P, Bruyere O, Al-Daghri N, Altman RD, et al. Use of intraarticular hyaluronic acid in the management of knee osteoarthritis in clinical practice. Arthritis Care Res 2017;69:1287—96.
[47] Bhadra AK, Altman R, Dasa V, Myrick K, Rosen J, Vad V, et al. Appropriate use criteria for hyaluronic acid in the treatment of knee osteoarthritis in the United States. Cartilage 2017;8:234—54.
[48] Abdulla A, Adams N, Bone M, Elliott AM, Gaffin J, Jones D, et al. Guidance on the management of pain in older people. Age Ageing 2013;42:i1—57.
[49] Maheu E, Bannuru RR, Herrero-Beaumont G, Allali F, Bard H, Migliore A. Why we should definitely include intra-articular hyaluronic acid as a therapeutic option in the management of knee osteoarthritis: results of an extensive critical literature review. Semin Arthritis Rheum 2018, http://dx.doi.org/10.1016/j.semarthrit.2018.06.002.
[50] Peterson C, Hodler J. Adverse events from diagnostic and therapeutic joint injections: a literature review. Skeletal Radiol 2011;40:5—12.
[51] Hunter DJ. Viscosupplementation for osteoarthritis of the knee. NEJM 2015;372:1040—7.
[52] Kroesen S, Schmid W, Theiler R. Induction of an acute attack of calcium pyrophosphate dihydrate arthritis by intra-articular injection of hylan G-F 20 (Synvisc). Clin Rheumatol 2000;19:147—9.
[53] Bannuru RR, Brodie CR, Sullivan MC, McAlindon TE. Safety of repeated injections of sodium hyaluronate (SUPARTZ) for knee osteoarthritis: a systematic review and meta-analysis. Cartilage 2016;7:322—32.
[54] Raman R, Henrotin Y, Chevalier X, Migliore A, Jerosch J, Montfort J, et al. Decision algorithms for the retreatment with viscosupplementation in patients suffering from knee osteoarthritis: recommendations from the EUROpean VIScosupplementation COnsensus Group (EUROVISCO). Cartilage 2018;9:263—75.
[55] He WW, Kuang MJ, Zhao J, Sun L, Lu B, Wang Y, et al. Efficacy and safety of intraarticular hyaluronic acid and corticosteroid for knee osteoarthritis: a meta-analysis. Int J Surg 2017;39:95—103.
[56] Navarro-Sarabia F, Coronel P, Collantes E, Navarro FJ, de la Serna AR, Naranjo A, et al. A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of

hyaluronic acid in knee osteoarthritis: the AMELIA project. Ann Rheum Dis 2011;70:1957—62.
[57] Altman R, Fredericson M, Bhattacharyya SK, Bisson B, Abbott T, Yadalam S, et al. Association between hyaluronic acid anjections and time-to-total knee replacement surgery. J Knee Surg 2016;29:564—70.
[58] Smith C, Patel R, Vannabouathong C, Sales B, Rabinovich A, McCormack R, et al. Combined intra-articular injection of corticosteroid and hyaluronic acid reduces pain compared to hyaluronic acid alone in the treatment of knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc 2018, http://dx.doi.org/10.1007/s00167-018-5071-7.
[59] Shen L, Yuan T, Chen S, Xie X, Zhang C. The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. J Orthop Surg Res 2017;12:16.
[60] Rayegani SM, Raeissadat SA, Taheri MS, Babaee M, Bahrami MH, Eliaspour D, et al. Does intra articular platelet rich plasma injection improve function, pain and quality of life in patients with osteoarthritis of the knee? A randomized clinical trial. Orthop Rev 2014;6:5405.
[61] Kabiri A, Esfandiari E, Esmaeili A, Hashemibeni B, Pourazar A, Mardani M. Platelet-rich plasma application in chondrogenesis. Adv Biomed Res 2014;3:138.
[62] Filardo G, Kon E, Roffi A, Di Matteo B, Merli ML, Marcacci M. Platelet-rich plasma: why intra-articular? A systematic review of preclinical studies and clinical evidence on PRP for joint degeneration. Knee Surg Sports Traumatol Arthrosc 2015;23:2459—74.
[63] Smith PA. Intra-articular autologusconditioned plasma injections provide safe and efficacious treatment for knee osteoarthritis: an FDA-sanctioned, randomized, double-blind, placebo-controlled clinical trial. Am J Sports Med 2016;44:884—91.
[64] 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.
[65] Khoshbin A, Leroux T, Wasserstein D, Marks P, Theodoropoulos J, Ogilvie-Harris D, et al. The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: a systematic review with quantitative synthesis. Arthroscopy 2013;29:2037—48.
[66] Lopa S, Colombini A, Moretti M, de Girolamo L. Injective mesenchymal stem cell-based treatments for knee osteoarthritis: from mechanisms of action to current clinical evidences. Knee Surg Sports Traumatol Arthrosc 2018, http://dx.doi.org/10.1007/s00167-018-5118-9.
[67] Moroni L, Fornasari PM. Human mesenchymal stem cells: a bank perspective on the isolation, characterization and potential of alternative sources for the regeneration of musculoskeletal tissues. J Cell Physio 2013;228:680—7.
[68] Lv FJ, Tuan RS, Cheung KM, Leung VY. Concise review: the surface markers and identity of human mesenchymal stem cells. Stem Cells 2014;32:1408—19.
[69] Atesok K, Fu FH, Sekiya I, Stolzing A, Ochi M, Rodeo SA. Stem cells in degenerative orthopaedic pathologies: effects of aging on therapeutic potential. Knee Surg Sports Traumatol Arthrosc 2017;25:626—36.
[70] Beane OS, Fonseca VC, Cooper LL, Koren G, Darling EM. Impact of aging on the regenerative properties of bone marrow-, muscle-, and adipose-derived mesenchymal stem/stromal cells. PloS One 2014;9:e115963.
[71] Cianfarani F, Toietta G, Di Rocco G, Cesareo E, Zambruno G, Odorisio T. Diabetes impairs adipose tissue-derived stem cell function and efficiency in promoting wound healing. Wound Repair Regen 2013;21:545—53.
[72] Sun Y, Deng W, Geng L, Zhang L, Liu R, Chen W, et al. Mesenchymal stem cells from patients with rheumatoid arthritis display impaired function in inhibiting Th17 cells. J Immunol Res 2015;2015:284215.
[73] Ranmuthu CDS, Ranmuthu CKI, Khan WS. Evaluating the current literature on treatments containing adipose-derived stem cells for osteoarthritis: a progress update. Curr Rheumatol Rep 2018;20:67.
[74] Al-Najar M, Khalil H, Al-Ajlouni J, Al-Antary E, Hamdan M, Rahmeh R, et al. Intra-articular injection of expanded autologous bone marrow mesenchymal cells in moderate and severe knee osteoarthritis is safe: a phase I/II study. J Orthop Surg Res 2017;12:190.
[75] McAlindon TE, Schmidt U, Bugarin D, Abrams S, Geib T, DeGryse RE, et al. Efficacy and safety of single-dose onabotulinumtoxinA in the treatment of symptoms of osteoarthritis of the knee: results of a placebo-controlled, double-blind study. Osteoarthritis Cartilage 2018;26:1291—2129.
[76] Arendt-Nielsen L, Jiang GL, DeGryse R, Turkel CC. Intra-articular onabotulinumtoxinA in osteoarthritis knee pain: effect on human mechanistic pain biomarkers and clinical pain. Scand J Rheumatol 2017;46:303—16.
[77] Lopes de Jesus CC, Dos Santos FC, de Jesus L, Monteiro I, Sant'Ana M, Trevisani VFM. Comparison between intra-articular ozone and placebo in the treatment of knee osteoarthritis: a randomized, double-blinded, placebo-controlled study. PloS One 2017;12:e0179185.
[78] Duymus TM, Mutlu S, Dernek B, Komur B, Aydogmus S, Kesiktas FN. Choice of intra-articular injection in treatment of knee osteoarthritis: platelet-rich plasma, hyaluronic acid or ozone options. Knee Surg Sports Traumatol Arthrosc 2017;25:485—92.
[79] Guermazi A, Kalsi G, Niu J, Crema MD, Copeland RO, Orlando A, et al. Structural effects of intra-articular TGF-beta1 in moderate to advanced knee osteoarthritis: MRI-based assessment in a randomized controlled trial. BMC Musculoskelet Disord 2017;18:461.
[80] Cherian JJ, Parvizi J, Bramlet D, Lee KH, Romness DW, Mont MA. Preliminary results of a phase II randomized study to determine the efficacy and safety of genetically engineered allogeneic human chondrocytes expressing TGF-beta1 in patients with grade 3 chronic degenerative joint disease of the knee. Osteoarthritis Cartilage 2015;23:2109—18.
[81] Ha CW, Cho JJ, Elmallah RK, Cherian JJ, Kim TW, Lee MC, et al. A multicenter, single-blind, phase IIa clinical trial to evaluate the efficacy and safety of a cell-mediated gene therapy in degenerative knee arthritis patients. Hum Gene Ther Clin Dev 2015;26:125—30.
[82] Iannaccone F, Dixon S, Kaufman A. A review of long-term pain relief after genicular nerve radiofrequency ablation in chronic knee osteoarthritis. Pain Physician 2017;20:E437—44.
[83] Hirasawa Y, Okajima S, Ohta M, Tokioka T. Nerve distribution to the human knee joint: anatomical and immunohistochemical study. Int Orthop 2000;24:1—4.
[84] Kennedy JC, Alexander IJ, Hayes KC. Nerve supply of the human knee and its functional importance. Am J Sports Med 1982;10:329—35.
[85] Choi WJ, Hwang SJ, Song JG, Leem JG, Kang YU, Park PH, et al. Radiofrequency treatment relieves chronic knee osteoarthritis pain: a double-blind randomized controlled trial. Pain 2011;152:481—7.
[86] McCormick ZL, Korn M, Reddy R, Marcolina A, Dayanim D, Mattie R, et al. Cooled radiofrequency ablation of the genicular nerves for chronic pain due to knee osteoarthritis: six-month outcomes. Pain Med 2017;1:1631—41.

[87] Gupta A, Huettner DP, Dukewich M. Comparative effectiveness review of cooled versus pulsed radiofrequency ablation for the treatment of knee osteoarthritis: a systematic review. Pain Physician 2017;20:155—71.
[88] Jamison DE, Cohen SP. Radiofrequency techniques to treat chronic knee pain: a comprehensive review of anatomy, effectiveness, treatment parameters, and patient selection. J Pain Res 2018;11:1879—88.
[89] Kim SY, Le PU, Kosharskyy B, Kaye AD, Shaparin N, Downie SA. Is genicularnNerve radiofrequency ablation safe? a literature review and anatomical study. Pain Physician 2016;19:E697—705.
[90] Hanakawa T. Neural mechanisms underlying deafferentation pain: a hypothesis from a neuroimaging perspective. J Orthop Sci 2012;17:331—5.
[91] Bittman RW, Peters GL, Newsome JM, Friedberg EB, Mitchell JW, Knight JM, et al. Percutaneous image-guided cryoneurolysis. AJR Am J Roentgenol 2018;210:454—65.
[92] Hsu M, Stevenson FF. Wallerian degeneration and recovery of motor nerves after multiple focused cold therapies. Muscle Nerve 2015;51:268—75.
[93] Guillot X, Tordi N, Prati C, Verhoeven F, Pazart L, Wendling D. Cryotherapy decreases synovial Doppler activity and pain in knee arthritis: a randomized-controlled trial. Joint Bone Spine 2017;84:477—83.
[94] Guillot X, Martin H, Seguin-Py S, Maguin-Gate K, Moretto J, Totoson P, et al. Local cryotherapy improves adjuvant-induced arthritis through down-regulation of IL-6/IL-17 pathway but independently of TNFalpha. PloS One 2017;12:e0178668.
[95] Radnovich R, Scott D, Patel AT, Olson R, Dasa V, Segal N, et al. Cryoneurolysis to treat the pain and symptoms of knee osteoarthritis: a multicenter, randomized, double-blind, sham-controlled trial. Osteoarthritis Cartilage 2017;25:1247—56.
[96] Okuno Y, Korchi AM, Shinjo T, Kato S. Transcatheter arterial embolization as a treatment for medial knee pain in patients with mild to moderate osteoarthritis. Cardiovasc Intervent Radiol 2015;38:336—43.
[97] Okuno Y, Korchi AM, Shinjo T, Kato S, Kaneko T. Midterm clinical outcomes and MR imaging changes after transcatheter arterial embolization as a treatment for mild to moderate radiographic knee osteoarthritis resistant to conservative treatment. J Vasc Interv Radiol 2017;28:995—1002.
[98] Nguyen C, Lefèvre-Colau MM, Poiraudeau S, Rannou F. Evidence and recommendations for use of intra-articular injections for knee osteoarthritis. Ann Phys Rehabil Med 2016;59:184—9.