

Arthroscopy Association of Canada Position Statement on Intra-articular Injections for Knee Osteoarthritis

Arthroscopy Association of Canada*†

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The Arthroscopy Association of Canada (AAC) recently published guidelines pertaining to arthroscopic surgery as a treatment for osteoarthritis (OA) of the knee. This was in response to recent public interest surrounding the utility and cost-effectiveness of arthroscopic surgery in this setting. As part of these guidelines, the AAC recommends a 6- to 9-month trial of “appropriate and comprehensive non-operative treatment.”⁵³ A key component of nonoperative strategies are intra-articular injections. The injections available in Canada include corticosteroids, hyaluronic acid (HA), platelet-rich plasma (PRP), and cellular-based therapies, including bone marrow aspirate concentrate (BMAC). In light of emerging evidence, the AAC endeavored to synthesize the most relevant and up-to-date data pertaining to the use of these agents in the treatment of knee OA. Based on the highest quality available evidence as well as the expert opinion of experienced clinicians, recommendations to help guide clinical practice are proposed. The grading of recommendations is categorized according to the scale developed by Wright et al⁵⁴ and subsequently expanded by Stevens et al⁴⁷ (Table 1). It is understood that the ultimate decision-making process will involve the treating clinician as well as the patient and will take into consideration all associated risks and benefits.

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CORTICOSTEROIDS

Synthetic corticosteroids have been used in clinical practice for over 50 years. Their anti-inflammatory effect is caused primarily by their ability to modulate the expression of lymphocytes and cytokines.¹⁶ They also serve to increase the viscosity and HA concentration of synovial fluid.²⁴ The most common injectable corticosteroids available include methylprednisolone and triamcinolone. They are often combined with a local anesthetic to decrease the incidence of a postinjection flare reaction, which can occur in 3% to 25% of injections.²¹

The most recent recommendations from the American Academy of Orthopaedic Surgeons (AAOS) synthesized the available literature up to 2013 and concluded that there is “inconclusive evidence to recommend for or against the use of intra-articular corticosteroids to treat knee OA.”²⁸ A 2015 Cochrane review found corticosteroids to be more beneficial than a control in reducing pain and improving function in the early (<6 weeks) postinjection period, with no benefit observed beyond 6 months.²⁹ However, the small sample size and poor methodological quality of the studies included significantly reduced the strength of these findings.²⁹ More recently, McAlindon et al³⁸ aimed specifically to determine the deleterious effects of repeated corticosteroid injections in patients with knee OA. Patients were randomized to receive intra-articular triamcinolone or saline injections every 3 months for 2 years. The authors showed no difference in pain scores between the 2 groups but an increase in cartilage volume loss on magnetic resonance imaging in the corticosteroid cohort.³⁸ Finally, a prospective multicenter trial evaluated the factors affecting the treatment response to intra-articular corticosteroids in patients with knee OA. That study revealed that patients with less severe OA (Kellgren-Lawrence grades 1-2) were more likely to achieve and maintain improvement up to 3 months after the injection. Obesity was also shown to decrease the treatment effect.³⁷

The evidence suggests that intra-articular corticosteroids possess moderate benefit in reducing pain and

TABLE 1
Grades of Recommendation for Summaries or Reviews of Orthopaedic Surgical Studies and a Proposed Subscale
Designed to Differentiate Evidence for Indications Receiving a Grade of Recommendation of C^a

Grades of Recommendation	Description
A	Good evidence (level 1 studies with consistent findings) for or against recommending an intervention
B	Fair evidence (level 2 or 3 studies with consistent findings) for or against recommending an intervention
C	Conflicting or poor-quality evidence (level 4 or 5 studies) not allowing a recommendation for or against an intervention
I	Insufficient evidence to make a recommendation

Proposed Subscale	Description
C _f	Representing literature “for,” or in support of, a surgical intervention
C _u	Representing literature “against,” or not in support of, a surgical intervention
C _e	Representing conflicting literature, some of which is in support of a surgical intervention and some of which is not in support of a surgical intervention

^aFrom Stevens MS, Legay DA, Glazebrook MA, Amirault D. The evidence for hip arthroscopy: grading the current indications. *Arthroscopy*. 2010;26(10):1370-1383.⁴⁷

improving function in the early stages of knee OA. The effects are most pronounced in the early time frame after injection and do not persist beyond 6 months. Although the risk of adverse events is relatively low, repeated injections should be performed with caution because of a risk of further cartilage volume loss.

Recommendation: Intra-articular corticosteroid injections provide short-term, moderate pain relief and the restoration of function and offer a cost-effective treatment option in patients with early knee OA. Strength of recommendation: Good – A

HYALURONIC ACID

HA is a naturally occurring polymer that has been shown to increase the viscosity of synovial fluid as well as the compressive strength of articular cartilage.⁴¹ In the setting of OA, it acts to decrease inflammation by reducing oxidative stress and inhibiting phagocytosis of macrophages.³⁰ HA has been approved in Canada for the treatment of mild to moderate OA of the knee since 1992. Accordingly, a number of preparations have become available, differing primarily in their method of production, molecular weight, cross-linking, and administration.³⁹ High-molecular weight (HMW) HA has been defined as greater than 3000 kDa, although some studies suggest that 6000 kDa is more likely to affect outcomes.^{3,6} Overall, HA possesses a relatively low-risk profile, with adverse reactions such as infection and granulomatous inflammation reported in 4% to 13% of injections.^{2,10}

Numerous randomized controlled trials (RCTs) have investigated the efficacy of HA in recent years. Unfortunately, significant heterogeneity in the trial design, preparation employed, and outcome measures assessed has challenged the interpretation of the results. In 2006, a Cochrane review concluded that HA provides pain reduction and improvement in physical function and is thus a viable treatment option in younger patients

with less severe OA.⁹ However, the 2013 AAOS Clinical Practice Guidelines²⁷ cited a strong recommendation against the use of HA for the treatment of knee OA. Recent studies have focused on the intrinsic properties of HA that influence outcomes. A systematic review by Rutjes et al⁴³ compared HA with placebo or no intervention. Upon subgroup analysis, HMW HA preparations showed both a statistically and clinically significant reduction in pain.⁴³ Subsequent meta-analyses have confirmed these results.^{3,6} A meta-analysis by Jevsevar et al²⁶ reported that highly cross-linked HA had a significantly greater treatment effect size than non-cross linked HA at 26 weeks after injection. Xing et al⁵⁵ conducted a systematic review of 12 meta-analyses and concluded that HA is an effective intervention for the treatment of knee OA without an increased risk of adverse events. In 2017, a group of Canadian clinicians and scientists met to review all meta-analyses of RCTs published between 2012 and 2016 comparing HA with placebo or no intervention.¹⁰ They concluded that intra-articular HA resulted in improved pain, function, and stiffness for up to 26 weeks in patients with mild to moderate knee OA. Furthermore, HMW HA was superior to low-molecular weight (LMW) HA and surpassed the threshold of the minimal clinically important difference (MCID).¹⁰ Similarly, a 2018 systematic review of all non-operative treatments for knee OA concluded that, after accounting for the intra-articular placebo effect, HMW HA had the most precise treatment effect, surpassing the MCID.⁵⁰

Although controversy persists in the literature, more recent evidence suggests that HA is superior to placebo or no intervention in providing pain relief and improving function in patients with knee OA. HMW and highly cross-linked HA are likely more effective than LMW and non-cross linked HA, respectively. The effects are most pronounced in mild to moderate disease and in the first 26 weeks after injection.

Recommendation: Intra-articular injections of HMW HA provide improved pain relief and the restoration of function compared with placebo and can be considered in patients with mild to moderate knee OA. Strength of recommendation: Good – A

PLATELET-RICH PLASMA

PRP was initially defined as “a volume of plasma with an above-baseline concentration of platelets.”³⁶ This definition has since changed, requiring PRP to contain a minimum of 1 million platelets per milliliter, which is thought to be the threshold required to stimulate targeted cells.^{36,40} PRP is derived from autogenous whole blood centrifugation, which separates out red blood cells, leaving PRP. Once injected, platelets degranulate, releasing proteins, cytokines, and growth factors that help regulate the inflammatory process and stimulate cell proliferation.^{20,25} A number of PRP preparation systems are commercially available, although each yields differences in platelet capture efficiency and the concentration of additional constituents (ie, white blood cells, growth factors, etc).¹⁹ In addition to the heterogeneity attributed to the preparation system, the PRP composition can also be affected by exercise and the time of day.⁵ This significant heterogeneity between preparations makes the interpretation of clinical results and pooling of data for meta-analyses extremely challenging.

In 2013, the AAOS Clinical Practice Guidelines reported insufficient evidence to support the use of PRP for knee OA.²⁸ However, research surrounding the use of PRP for knee OA has progressed in recent years. Several RCTs have compared PRP with placebo (saline) and other intra-articular therapies, including HA and corticosteroids. A recent meta-analysis evaluated 10 RCTs comparing PRP with placebo (saline) and HA.¹⁸ Compared with placebo (saline), PRP showed significantly better improvements in pain and function at both 6 and 12 months, with effect sizes exceeding the MCID. While PRP and HA had similar positive effects in improving pain and function at 6 months, PRP demonstrated superior outcomes to HA at 12 months for both pain relief and functional improvement. The effect sizes for both measures also exceeded the MCID. Along the same lines as this meta-analysis, a recent RCT by Cole et al¹⁷ evaluated 111 patients with knee OA who received either leukocyte-poor PRP or HA. Although they showed no difference in the primary outcome (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]), improvements favoring leukocyte-poor PRP were seen in International Knee Documentation Committee and visual analog scale scores.¹⁷ Additional studies have also shown that patient age and the stage of OA can influence the efficacy of PRP, with younger patients with lower grade OA (Kellgren-Lawrence grades 1-2) demonstrating comparatively better outcomes.^{11,22} Overall, PRP has been shown to have a low risk of adverse reactions, with studies showing no difference between intra-articular injections of PRP and placebo.³¹

Despite the improved quality of evidence to provide some support for PRP in knee OA, heterogeneity in outcomes exists, and many questions remain. There is still little

information on the optimal preparation system and preparation method, composition (ie, leukocyte-rich or leukocyte-poor), clinical dosage required, and durability of achieved results. Combined with the aforementioned heterogeneity introduced by the different commercially available preparation systems, a consensus for recommended use remains challenging.

Recommendation: PRP injection has the potential to provide improvements in pain and functional outcomes up to 1 year after the injection in patients with mild to moderate knee OA. Evidence of efficacy in advanced OA is lacking. Given the heterogeneity of the evidence as well as the lack of consensus on the ideal PRP preparation method and composition, we cannot recommend for or against the use of PRP until further high-quality clinical studies become available. Strength of recommendation: C_r

CELLULAR-BASED THERAPIES: BMAC

Cellular-based therapies using undifferentiated progenitor cells, or stem cells, have become an attractive potential option for treating OA and chondral injuries of the knee. The rationale for their use is that these mesenchymal stem cells (MSCs) may be able to differentiate into cells of a chondrogenic lineage, contributing to restorative healing.⁴⁹ Some studies have even reported that they possess the capacity to help regenerate subchondral bone in small defects.³⁴ However, other theories attribute their clinical effect to their strong anti-inflammatory properties rather than their regenerative potential.³⁴ Caplan¹³ suggested changing the name to “medicinal signaling cells” to reflect their ability to migrate to sites of injury and secrete therapeutic (“medicinal”) factors.

MSCs can be isolated from a variety of tissues, including adipose, amniotic fluid/membrane, and bone marrow.⁴⁰ Presently, Health Canada has only approved stem cell use in the treatment of certain oncological processes. Health Canada does not currently regulate the use of stem cells in a homologous manner with minimal manipulation, allowing unapproved use for certain musculoskeletal conditions. This is akin to the regulations by the Food and Drug Administration (FDA) in the United States. As a result of the control of these regulatory bodies, the use of cultured or manipulated stem cells has been limited to controlled phase 1/2 clinical studies. Bone marrow-derived MSCs have been the primary focus of most studies, while adipose-derived cells and the stromal vascular fraction are starting to receive more attention. While there are several small series demonstrating clinical and radiological improvements after intra-articular injections of stem cells from each of these sources for the treatment of knee OA, the small sample sizes and heterogeneity of patients and cellular concentrations make it difficult to draw meaningful conclusions.³⁵

In recent years, BMAC without additives, culturing, or expansion has been considered to comply with Health Canada and FDA standards of “minimal manipulation.”⁴⁵ As such, it has been increasingly used, as it allows for simple retrieval and the utilization of bone marrow-derived

MSCs, despite the fact that MSCs comprise only a minor proportion of BMAC (0.001%-0.01%).¹⁵ It may be that the various cellular components of BMAC are equally or more important than the MSCs themselves. This is particularly true of interleukin-1 receptor antagonist (IL-1ra), which is present in high concentrations and acts as a potent anti-inflammatory agent by inhibiting IL-1 catabolism.¹⁴ Two recent RCTs compared BMAC with placebo (saline injection) in the treatment of knee OA.^{44,45} Both identified significant improvements in pain and quality of life 12 months after BMAC injection; however, these results did not differ significantly from the response to saline injections in the contralateral knee. Another study demonstrated that there was a significant association between a higher Kellgren-Lawrence grade and inferior outcomes.³² Additional studies have also utilized BMAC; however, the interpretation of the results has remained challenging, as BMAC is often utilized with concomitant surgical procedures or interventions.⁵¹ Furthermore, there is no consensus on the BMAC harvest technique, concentration, or effective clinical dosage. As a result, consensus recommendations are similarly not feasible, and current use should be limited to clinical trials rather than routine clinical use. While we do recognize the potential benefit of biological therapies, rigorous, well-designed clinical trials are needed to establish the safety, efficacy, and cost-effectiveness of these potential treatments before widespread adoption.

Recommendation: There is insufficient evidence to support the use of MSCs or BMAC in the treatment of knee OA. As such, MSC and BMAC injections should be limited to registered controlled trials, and we cannot recommend their use in routine clinical practice until further evidence becomes available. Strength of recommendation: Insufficient – I

COMBINATION THERAPIES

The combination of various intra-articular injection therapies has been investigated in recent years. More specifically, 4 combinations have been reported in the literature: HA and corticosteroids, HA and PRP, PRP and corticosteroids, and PRP and MSCs.

The most frequently described combination therapy is HA with corticosteroids. Studies have shown that intra-articular corticosteroid injections have a rapid onset of action with a short overall duration, while HA injections have a slower onset but provide longer lasting benefits.^{6,7} Accordingly, combining HA with corticosteroids may offer quicker and more durable pain relief than either agent alone. A 2019 meta-analysis by Smith et al⁴⁶ identified 8 RCTs comparing intra-articular injections of combined HA and corticosteroids to HA alone in the treatment of knee OA. The HA plus corticosteroid group showed improved WOMAC pain scores at 2 to 4 weeks, 24 to 26 weeks, and 52 weeks after injection compared with the HA-only group. There were no significant differences in pain scores at intermediate follow-up (6-13 weeks) or in treatment-related adverse events at any time point. Two more recent RCTs have since been published. Both studies report

improvement in WOMAC pain scores for combined HA and corticosteroid injections at earlier time points (6-12 weeks), with no difference at longer term follow-up (26 weeks).^{23,52} Despite the promising results favoring intra-articular injections of combined HA and corticosteroids in the treatment of knee OA, these findings must be met with caution, as they are limited by the small number of high-quality studies, heterogeneity in reported outcomes, and paucity of data comparing HA and corticosteroids with placebo. Concerns regarding the potential acceleration of cartilage loss with serial cortisone injections outlined above also apply to combination therapy.

The use of HA in combination with PRP has also been reported in recent years. As outlined above, both agents have shown benefit in the treatment of early knee OA, although they differ in their mechanism of action. Basic science studies confirm that PRP, along with its anti-inflammatory and immunomodulatory role, can also stimulate HA production. Accordingly, PRP with HA may have a synergistic effect in the creation of a favorable medium for cellular healing, and combination therapy may be superior to a single agent alone.^{4,48} Unfortunately, this hypothesis has not been borne out in the literature. Current studies regarding intra-articular injections of combined HA and PRP show inconsistent results and are of poor methodological quality.^{1,33,56} In the absence of high-level evidence, we cannot recommend combination therapy with HA and PRP at this time.

Studies investigating combination therapies with PRP and corticosteroids and with PRP and MSCs are limited to small case series and pilot studies and are not of sufficient quality to warrant further consideration at this time.^{8,12,42}

Recommendation: (1) Intra-articular injections of combined HA and corticosteroids in the setting of knee OA can provide significant improvement in pain outcomes and may provide a more rapid onset and longer duration of action than either therapy alone. Strength of recommendation: Fair – B

(2) There is insufficient evidence to support other combinations of intra-articular injection therapy. Strength of recommendation: Insufficient – I

POSITION STATEMENT CONCLUSIONS

1. Intra-articular corticosteroid injections provide short-term, moderate pain relief and the restoration of function.²⁹
2. Intra-articular HA provides improvement in pain, function, and stiffness for up to 26 weeks after an injection in patients with mild to moderate knee OA. It is safe with a low risk of adverse events.^{9,43,55}
3. HMW HA is superior to LMW HA, with a treatment effect surpassing the MCID.⁵⁰ Similarly, highly cross-linked HA is more effective than non-cross linked HA.²⁶
4. PRP is safe with a low risk of adverse events. Although some studies identify the potential to improve pain and function, its therapeutic effect in early knee OA has been shown to be highly variable and without

clear proven benefits. As such, there is insufficient evidence at this time to recommend for or against the use of PRP.^{18,31}

5. There is insufficient evidence comparing PRP compositions (ie, leukocyte-rich vs leukocyte-poor) to make definitive recommendations for the treatment of knee OA.
6. There is insufficient evidence to recommend MSCs/BMAC in the treatment of knee OA.
7. Rigorous, well-designed clinical trials are needed to establish the safety, efficacy, and cost-effectiveness of BMAC/MSCs before widespread adoption.
8. Combination therapy with HA and corticosteroids has been shown to significantly reduce pain in knee OA, with a more rapid onset of action than HA alone.⁴⁶
9. The use of any injectables is most effective in patients with mild to moderate knee OA (Kellgren-Lawrence grades 1-2).
10. The use of injectables for knee OA should take into consideration evidence-based research and a discussion of the efficacy, safety, and cost-effectiveness of such treatments within the patient's means.

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