Arthroscopy Association of Canada (AAC) Position Statement on Intra-Articular Injections for Knee Osteoarthritis

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Conflict of Interest Statement
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Introduction
The Arthroscopy Association of Canada (AAC) recently published guidelines pertaining to arthroscopy 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 six to nine-month trial of “appropriate and comprehensive non-operative treatment.” A key

component of non-operative 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 concentration (BMAC). In light of emerging evidence, the AAC endeavoured to synthesize the most relevant and up-to-date data pertaining to the use of these agents in the treatment of knee OA. Based upon 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 al. and subsequently expanded by Stevens et al. (Table 1)[1, 2] 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. The Arthroscopy Association of Canada, and Canadian Orthopaedic Association recently reviewed the most up to date evidence on the use of these injections.

Corticosteroids

Synthetic corticosteroids have been used in clinical practice for over 50 years. Their anti-inflammatory effect is due primarily to their ability to modulate the expression of lymphocytes and cytokines.[3] They also serve to increase the viscosity and hyaluronic acid concentration of synovial fluid.[4] The most common injectable corticosteroids available include methylprednisolone and triamcinolone. They are often combined with local anaesthetic to decrease the incidence of a post-injection flare reaction that can occur in 3-25%.[5]

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.”[6] A 2015 Cochrane review found corticosteroids to be more beneficial than controls in reducing pain and improving function in the early (<6 weeks) time frame post-injection with no benefit observed beyond 6 months. However, the small size and poor methodological quality of the studies significantly reduced the strength of these findings.[7] More recently, McAlindon et al. 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 three months for two years. The authors showed no difference in pain scores between the two groups, but an increase in cartilage volume loss on MRI in the corticosteroid cohort.[8] Finally, a prospective multi-center trial evaluated the factors affecting treatment response to intra-articular corticosteroid in patients with knee OA. This revealed that patients with less severe OA (Kellgren-Lawrence grades I-II) were more likely to achieve and maintain improvement up to 3 months post injection. Obesity was also shown to decrease treatment effect.[9]

The evidence suggests that intra-articular corticosteroids possess moderate benefit in reducing pain and improving function in early stages of knee OA. The effects are most pronounced in the early time frame post-injection and do not persist beyond 6 months.

Though the risk of adverse events is relatively low, repeated injections should be performed with caution due to a risk of further cartilage volume loss.

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

Hyaluronic Acid

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.[10] In the setting of osteoarthritis, it acts to decrease inflammation by reducing oxidative stress and inhibiting phagocytosis of macrophages.[11] 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.[12] High molecular weight HA (HMW-HA) has been defined as greater than 3000kDa, though some studies suggest that 6000kDa is more likely to affect outcome.[13, 14] Overall, HA possesses a relatively low risk profile, with adverse reactions such as infection and granulomatous inflammation reported in 4-13%.[15, 16]

Numerous RCTs have investigated the efficacy of HA in recent years. Unfortunately, significant heterogeneity in trial design, preparation employed, and outcome measures assessed have 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.[17] However, the 2012 AAOS Clinical Practice Guidelines cited a strong recommendation against the use of HA for the treatment of knee OA.[18] Recent studies have focused on the intrinsic properties of HA that influence outcomes. A systematic review by Rutjes et al. compared HA to placebo or no-intervention. Upon subgroup analysis, HMW-HA preparations showed both a statistically and clinically significant reduction in pain.[19] Subsequent meta-analyses have confirmed these results.[13, 14] A meta-analysis by Jevsevar et al. reported that highly cross-linked HA had significantly greater treatment effect size than non-cross-linked HA at 26 weeks post-injection.[20] Xing et al. 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.[21] In 2017, a group of Canadian clinicians and scientists met to review all meta-analyses of randomized controlled trials published between 2012 and 2016 comparing HA to placebo or no-intervention. They concluded that intra-articular HA resulted in improvement in pain, function, and stiffness up to 26 weeks in patients with mild to moderate knee OA. Furthermore, HMW-HA was superior to LMW-HA and surpassed thresholds of minimum clinically important difference (MCID).[16] 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.[22]

Though 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. High molecular weight and highly cross-linked HA are likely more effective than low molecular weight and non-cross-linked HA, respectively. The effects are most pronounced in mild to moderate disease, and in the first 26 weeks post-injection.

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

Platelet Rich Plasma (PRP)

Platelet Rich Plasma (PRP) was initially defined as "a volume of plasma with an above-baseline concentration of platelets." This definition has since changed, requiring PRP to contain a minimum of one million platelets per milliliter, which is thought to be the threshold required to stimulate targeted cells.[23, 24] PRP is derived from autogenous whole blood centrifugation, which separates out red blood cells leaving platelet-rich plasma. Once injected, platelets degranulate releasing proteins, cytokines and growth factors that help regulate the inflammatory process and stimulate cell proliferation.[25, 26] A number of PRP preparation systems are commercially-available, although each yields differences in platelet capture efficiency, and the concentration of additional constituents (i.e white blood cells, growth factors etc.).[27] In addition to the heterogeneity attributed to the preparation system, PRP composition can also be affected by exercise and the time of day.[28] This significant heterogeneity between preparations makes the interpretation of clinical results and pooling of data for meta-analyses extremely challenging.

In 2012, the AAOS Clinical Practice Guidelines reported insufficient evidence to support the use of PRP for knee OA.[6] However, research surrounding the use of PRP for knee OA has progressed in recent years. Several randomized controlled trials (RCTs) have compared PRP with placebo (saline) and other intra-articular therapies, including HA and corticosteroid. A recent meta-analysis evaluated 10 RCTs comparing PRP to placebo (saline) and HA.[29] Compared to 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 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 al. evaluated 111 patients with knee OA, who received either leukocyte poor (LP)-PRP or HA.[30] Though they showed no difference in the primary outcome (WOMAC), improvements favouring LP-PRP were seen in IKDC and VAS scores. Additional studies

have also shown that patient age and the stage of OA can influence the efficacy of PRP, with younger individuals with lower grade OA (Kellgren-Lawrence stage I and II) demonstrating comparatively better outcomes.[31, 32] 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.[33]

Despite 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 (i.e. leukocyte-rich or leukocyte-poor), clinical dosage required and the durability of achieved results. Combined with the aforementioned heterogeneity introduced by the different commercially-available preparation systems, consensus agreement for recommended use remains challenging.

Recommendation: PRP injection has the potential to provide improvements in pain and functional outcomes up to one-year post 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 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: Cf

Cellular-Based Therapies – Bone Marrow Aspirate Concentrate

Cellular-based therapies using undifferentiated progenitor cells, or stem cells, have become an attractive potential option for treating osteoarthritis 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.[34] Some studies have even reported that they possess the capacity to help regenerate subchondral bone in small defects.[35] However, other theories attribute their clinical effect to their strong anti-inflammatory properties, rather than their regenerative potential.[35] Caplan et al. suggested changing the name to “medicinal signalling cells” to reflect their ability to migrate to sites of injury and secrete therapeutic (“medicinal”) factors.[36]

MSCs can be isolated from a variety of tissues, including adipose, amniotic fluid/membrane and bone marrow.[24] Presently, Health Canada has only approved stem cell use in the treatment of certain oncologic 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 I/II 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 radiologic improvements following intra-articular injection of stem cells from each of these sources for the treatment of knee OA, the small sample size and heterogeneity of patients and cellular concentrations make it difficult to draw meaningful conclusions.[37]

In recent years, concentration of bone marrow aspirate (BMAC) without additives, culturing or expansion, has been considered to comply with Health Canada and FDA standards of 'minimal manipulation'.[38] As such, it has been increasingly used as it allows for simple retrieval and utilization of bone marrow derived MSCs, despite the fact that the MSCs comprise only a minor proportion of the BMAC (0.001-0.01%).[39] 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.[40] Two recent RCTs compared BMAC with placebo (saline injection) in the treatment of knee OA[38, 41]. Both identified significant improvements in pain and quality of life 12 months following BMAC injections, however these results did not differ significantly from their response to saline injections in their contralateral knee. Another study demonstrated that there was a significant association between a higher Kellgren-Lawrence grade and inferior outcomes. Additional studies have also utilized BMAC, however interpretation of the results has remained challenging as BMAC is often utilized with concomitant surgical procedures or interventions.[42] Furthermore, there is no consensus on BMAC harvest techniques, 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 biologic therapies, rigorous, well-designed clinical trials are needed to establish the safety, efficacy, and cost-effectiveness of these potential treatments prior to widespread adoption.

Recommendation: There is insufficient evidence to support the use of MSC 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, four combinations have been reported in the literature: hyaluronic acid and corticosteroid (HA/CS), hyaluronic acid and platelet rich plasma (HA/PRP), platelet rich plasma and corticosteroid (PRP/CS), and platelet rich plasma and mesenchymal stem cells (PRP/MSCs).

The most frequently described combination therapy is HA/CS. 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.[13, 43] Accordingly, combining HA with corticosteroid may offer quicker and more durable

pain relief than either agent alone. A 2018 meta-analysis by Smith et al. identified eight RCTs comparing intra-articular injection of combined HA/CS to HA alone in the treatment of knee OA.[44] The HA/CS group showed improved WOMAC pain scores at 2-4 weeks, 24-26 weeks, and 52 weeks post injection compared to 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/CS injections at earlier time points (6-12 weeks) with no difference at longer term follow up (26 weeks).[45, 46] Despite the promising results favoring intra-articular injection of combined HA/CS 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 a paucity of data comparing HA/CS to placebo. The concerns regarding 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 though 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 and 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.[47, 48] Unfortunately, this hypothesis has not been borne out in the literature. Current studies regarding intra-articular injection of combined HA/PRP show inconsistent results and are of poor methodological quality.[49-51] In the absence of high level evidence, we cannot recommend combination therapy with HA and PRP at this time.

Studies investigating combination therapy with PRP/CS and PRP/MSCs are limited to small case series and pilot studies and are not of sufficient quality to warrant further consideration at this time.[52-54]

Recommendation: (1) Intra-articular injection of combined HA/CS 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 restoration of function.[7]
2. Intra-articular hyaluronic acid provides improvement in pain, function, and stiffness for up to 26 weeks post injection in patients with mild to moderate knee osteoarthritis. It is safe with low risk of adverse events.[17, 19, 21]
3. High molecular weight hyaluronic acid is superior to low molecular weight hyaluronic acid with a treatment effect surpassing the minimum clinically important difference.[22] Similarly, highly cross-linked hyaluronic acid is more effective than non-cross-linked hyaluronic acid.[20]
4. Platelet rich plasma is safe with low risk of adverse events. Although some studies identify the potential to improve pain and function, the therapeutic effect in early knee osteoarthritis 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.[29, 33].
5. There is insufficient evidence comparing platelet rich plasma composition (i.e. leukocyte-rich vs. leukocyte-poor) to make definitive recommendations for the treatment of knee osteoarthritis.
6. There is insufficient evidence to recommend MSC/BMAC in the treatment of knee osteoarthritis.
7. Rigorous, well-designed clinical trials are needed to establish the safety, efficacy, and cost-effectiveness of BMAC/MSC prior to widespread adoption.
8. Combination therapy with hyaluronic acid/corticosteroid has been shown to significantly reduce pain in knee osteoarthritis, with a more rapid onset of action that hyaluronic acid alone.[44]
9. The use of any injectables are most effective in patients with mild to moderate knee OA (Kellegren Lawrence I-II)
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 patients means.

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

	Description
Grades of Recommendation	
A	Good evidence (Level I studies with consistent findings) for or against recommending intervention
B	Fair evidence (Level II or III studies with consistent findings) for or against recommending intervention
C	Conflicting or poor-quality evidence (Level IV or V studies) not allowing a recommendation for or against intervention.
I	Insufficient evidence to make a recommendation
Proposed subscale	
C_f	Representing literature "for," or in support of, a surgical intervention
C_a	Representing literature "against," or not in support of, a surgical intervention
C_c	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

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