Evidence-Based interventional approaches for management of knee osteoarthritis: A mini-review

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Abstract

Knee osteoarthritis (KOA) has a prevalence of 3.5% in Southeast Asian region. It is associated with pain and disability, affecting women more than men. Multiple non-surgical treatment options are available for pain management including oral analgesics, physical modalities, and interventional procedures (intra-articular injections, and denervation of knee joint). The evidence regarding various types of interventional procedures varies in literature. This mini review aims to present the latest evidence regarding interventional procedures for management of patients with KOA. The interventions can be broadly classified into Interventions with regenerative potential (e.g. platelet rich plasma, stem cell injections etc) and Interventions without regenerative potential (intra-articular steroid injections, denervation of knee joint etc). Intra-articular corticosteroids may be used in patients with KOA for short term relief . Nerve ablation techniques may provide moderate, short-term pain relief especially in advanced KOA, but the evidence is limited. Interventions with regenerative potential like PRP may be effective in pain relief and function, but there is heterogeneity in studies. Current evidence shows that MSCs may be promising for KOA, but it is still in an experimental phase.

Keywords: Platelet-Rich Plasma; Mesenchymal Stem Cells; Hyaluronic Acid; Botulinum Toxins, Type A; Knee Joint; Rehabilitation; Pain Measurement; Intra-Articular Injections.

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Introduction

The prevalence of Knee Osteoarthritis (KOA) in Southeast Asian region is 3.5%, with 3399.9 cases per 100,000 population[1]. KOA has 11.53 million DALYs, globally.[1] Females have a higher risk of developing KOA.[2] Obesity, history of trauma, static alignment of knee (varus or valgus), sports (soccer and long distance running) and femur-acetabular impingement are some of the risk factors for developing KOA.[2]

KOA is a degenerative joint disease which starts from the activation of humoral and cellular inflammatory mediators from the fibroblasts in the synovial membrane.[2] The resultant cytokines damage the cartilage which produces 'damage associated molecular patterns' (DAMPs).[2] DAMPs further propagate the inflammatory response by the fibroblasts, releasing cytokines and damaging the cartilage.[2] This vicious cycle between synovial membrane, cartilage and DAMPs plays a crucial role in pathogenesis of KOA.[2]

Multiple options for management of KOA exist, including pharmacological options, interventional procedures, and surgery. This mini review aims to summarize the latest evidence regarding interventional procedures for management of KOA.

Classification of Interventional Procedures:

For this review, the interventions are divided into : Non-regenerative Interventions and Regenerative Interventions.

A. Non-Regenerative Interventions: The interventions which do not have regenerative potential include:

1. Intra-articular Steroids: Intra-articular steroids are commonly used for management of KOA. In a systematic review and meta-analysis, intra-articular steroids resulted in pain relief and improved function at short term follow up (6weeks) only.[3] The effects reversed at medium (6-24 weeks) and long term (>24 weeks) follow up.[3] Intra-articular steroid was associated with greater reduction of cartilage thickness as compared to control (–0.21 vs–0.10 mm; between-group difference, –0.11 mm; 95% CI, –0.20 to –0.03 mm).[3]

2. Viscosupplementation (Hyaluronic acid-HA): The used of intra-articular hyaluronic acid (also known as Viscosupplementation) is controversial.[4] However, it is still

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used commonly and often as a first line treatment for advanced osteoarthritis despite clear recommendations. In a meta-analysis., a small, clinically non-significant decrease in pain was seen among patients treated with hyaluronic acid (HA) for KOA (SMD -0.85, CI -0.15 to -0.02, P=0.02).4 Similarly, there was non-clinically important improvement in function among these patients (SMD −0.11, 95% CI −0.18 to −0.05, P=0.001).[4] There was a statistically significant increased risk of serious adverse events in patients treated with Viscosupplementation (Relative Risk 1.49, 95% CI 1.12 to 1.98, P=0.003).[4]

3. Acupuncture / Electro-acupuncture (EA): Acupuncture is a Traditional Chinese Medicine approach used for management of pain in KOA. In a recent systemic review and network meta-analysis acupuncture resulted in pain improvement as compared to sham acupuncture (SMD -0.74, 95%CI -1.08 to -0.39).[5] The level of certainty was very low. Acupuncture also resulted in better physical function (SMD -0.77, 95%CI -1.21 to -0.34) with very low certainty evidence.[5] In this review, the number of acupoints varied, with most trials used 4 to 9 acupoints (85% of 66 trials).[5] Similarly, duration of acupuncture treatment varied from 5 days to 26 weeks.[5] EA had better pain relief as compared to manual acupuncture (SMD -0.75, 95%CI -1.34 to -0.17).[5] The same review also found that acupuncture was superior to NSAIDs.[5] There was no difference on pain when acupuncture was compared to intra-articular injection.[5] However, the risk of bias was very high in majority of the trials (85% of trials) included in this review and level of certainty was very low for all the findings of this review.[5]

4. Denervation of Knee Joint: For pain management in advanced osteoarthritis, genicular nerves are often targetted. The superiomedial, superiolateral, and inferomedial genicular nerves are commonly involved. Interventions include nerve blocks with local anaesthetics, radiofrequency ablation (RFA), cryo-neurolysis, or alcohol neurolysis. The results of these methods remain controversial. In a metanalysis by low uncertainty evidence suggested that RFA resulted in moderate pain reduction as compared to sham at 4 weeks (MD −1.70, 95% CI −3.03 to −0.36) and 12 weeks (MD −1.86, 95% CI −2.82 to −0.89) only.[6] When compared with simple Genicular Nerve Block (GNB), very low certainty evidence suggested that RFA resulted in small improvement in pain at 12 weeks (MD −1.70, 95% CI −2.10 to −1.30).[6] There was no statistical difference in pain and function, when RFA and GNB was compared with alcohol neurolysis.[6]

5. Botulinum toxin Injection: Recently, Botulinum Toxin Type A (BoNT-A) has been studied in experimental models to have anti-nociceptive effects be reduction in cytokines, neuropeptides and other inflammatory mediators.[7] Gagniere et al. conducted a systematic review and meta-analysis to compare the difference in pain and function between intra-articular BoNT-A and other intra-articular substances (e.g steroids, dextrose, hyaluronic acid) among patients with KOA.[7] There was no statistically significant difference in reduction of pain and activity limitations between BoNT-A and other groups at short term, mid-term and long-term.[7]

B. Regenerative Interventions:

1. Platelet Rich Plasma (PRP): PRP is a concentrate of platelets, produced from patient's own blood. Platelets release growth factors, cytokines and chemokines which result in cartilage regeneration and relief of symptoms of KOA.[8] In a recent systematic review and meta-analysis, PRP resulted in clinically and statistically significant improvement in WOMAC score at 12 months of follow-up as compared to placebo (Mean Difference[MD] -19.38, 95%CI, -36.04, -2.72) and hyaluronic acid (MD -11.34, 95%CI, -14.78, -7.91).[8] Moreover, clinically and statistically significant improvement in pain, function and quality of life were documented with PRP as compared to steroids.[8] There was no difference in adverse effects of PRP vs placebo.[8] It is important to note that these improvements were not significant at 1 month after PRP, and became increasingly significant starting from 6 month to 12 months of follow up. NSAIDs use during PRP sessions should be discouraged due to its anti-platelet effects. Patients need to be counselled that PRP benefits start to occur at least 6 months after the treatment and continue to increase thereafter.[8] This is necessary to manage patient's perception of the benefit of the treatment and in decision making.

2. Bone Marrow Aspirate Concentrate (BMAC): BMAC has recently gained interest as a management option of KOA with regenerative potential. It is commonly harvested from tibia, centrifuged and then administered in the knee joint.[9] In a meta-analysis ,BMAC resulted in improved WOMAC scores versus HA (SMD, 0.9803; 95% CI, 0.68331.2774; P < .001).[9] When compared with PRP, BMAC did not result in statistical significant WOMAC scores (SMD, 0.0773; 95% CI, e0.2217 to 0.3763) suggesting comparable results with both treatment options.[9] Similarly, pain decreased in patients treated with BMAC versus HA (SMD, 0.37, 95% CI, 0.0310-0.7081; P-value= 0.032).[9] No difference in pain was noted in patients receiving BMAC versus PRP (SMD, e0.24; 95% CI, e0.6022 to 0.1227; P-value= 0.19).[9]

3. Adipose-Derived Mesenchymal Stem Cells (AD-

MSCs): MSCs improve pain, stiffness, function and total WOMAC scores in patients with KOA (MD = 7.44, 95% CI = (1.45, 13.42), P = 0.01).[10] There was a statistical significant difference in improvement of WOMAC scores with AD-MSCs versus Bone marrow derived MSCs (MD = 7.53; 95%CI= (4.42,10.63); P < 0.0001).[10] Similarly, there was statistical significant improvement in pain when MSCs were used as compared to control group (MD = 19.39, 95% CI = (8.10, 30.68), P = 0.0008).[10]

4. Oxygen-Ozone Therapy (OOT): KOA is associated with chronic oxidative stress. Ozone has been shown to precondition the knee joint with oxidative stress, hence activating anti-oxidant pathways resulting in a paradoxical anti-oxidant effect.[11] However, the evidence regarding its efficacy is very limited. In a systematic review by Sconza et al., there was inconsistency between the documented outcomes, poor quality and bias of all the included studies, which made it difficult to make an assessment regarding comparison of ozone with standard treatments. Hence the use of OOT is still considered experimental.[11]

5. Dextrose Prolotherapy: The mechanism of action of dextrose prolotherapy is not completely understood. It is thought to induce a local inflammatory reaction, resulting in proliferation and remodeling of local tissues leading to healing of tissues.[12] In a recent systematic review by Wee et al., there was heterogeneity among the studies with respect to injection site and increased risk of bias. When compared with control, Dextrose prolotherapy improved function and reduced pain.[12] There was no statistical difference in pain and function, between dextrose prolotherapy and PRP.[12] In a meta-analysis by Wan et al., dextrose prolotherapy improved total WOMAC scores (WMD = 13.77, 95% CI: 6.75–20.78; p< 0.001; I2 = 90%) at 5 months.[13] The overall risk of bias in this meta-analysis was medium. Two of the five studies included in this trial had high risk of performance bias and detection bias.[13]

Evidence from Guidelines:

International guidelines including those from American College of Rheumatology (ACR) 2019, American Academy of Orthopedic Surgeons (AAOS) 2021 and National Institute of Health Care Excellence (NICE) 2022 provide varying recommendations for KOA management.[14-16] Table 1 summarized these guidelines to facilitate evidence-based decision-making in clinical practice.

Relevance to Pakistan:

Almost all interventions mentioned here are now available in Pakistan. However, they are mostly limited to major cities and are offered by multiple specialties and even non-physicians in a variety of settings. It is important that clinicians managing patients with KOA cautiously evaluate the hype created regarding certain interventions with evidence available in literature. Patient selection is an important criterion for success of these procedures and a detailed discussion with the patients and their

Table : Summary of Recommendations for interventional management of KOA by ACR-2019, AAOS-2021 and NICE-2022.

Intervention	ACR 2019	AAOS 2021	NHS/NICE (2022)	Comments
Intra-articular Corticosteroids	Strong recommendation (short-term relief)	Strong recommendation (short-term relief)	Recommended for short term relief	Effective in acute flare only
Hyaluronic Acid (Viscosupplementation)	Strong Recommendation against used	Strong recommendation against use	Not recommended	Evidence inconsistent; cost-effectiveness questioned
Acupuncture	Conditional recommendation	Limited recommendation	Not recommended	Heterogeneity in trials
Denervation/Genicular Nerve Blocks / RFA	Conditional recommendation	Limited recommendation (RFA: selective use in advanced OA)	Not mentioned	Used in refractory cases; growing interest
Botulinum Toxin	Conditional recommendation against use	Not recommended	Not mentioned	Limited evidence
Platelet-Rich Plasma (PRP)	Strong Recommendation against (due to lack of standardization in available preparations)	Limited recommendation	Not routinely recommended	Emerging evidence, but heterogeneity in trials
Mesenchymal Stem Cells (MSC)	Strong recommendation against use	Not mentioned	Not mentioned	Still under clinical trials phase
Ozone Therapy	Not mentioned in the guideline	Not mentioned	Not mentioned	Evidence inconsistent; Heterogeneity in trials
Dextrose Prolotherapy	Conditional recommendation against use	Not mentioned	Not mentioned	Heterogeneity in trials

caregivers on the advantages and limitations of these procedures can help improve pain management strategies in patients with KOA in Pakistan.

Conclusion

Intra-articular corticosteroids offer short-term relief for KOA patients, while nerve ablation can provide moderate, temporary pain relief in advanced cases. Strong evidence suggests avoiding intra-articular hyaluronic acid due to its adverse effects and limited benefits. Regenerative treatments like PRP may help with pain and function, though study results vary. MSCs show promise for KOA but remain experimental.

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