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General

A comprehensive review of intraarticular knee injection therapy, geniculate injections, and peripheral nerve stimulation for knee pain in clinical practice

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The knee is the most common joint in adults associated with morbidity. Many pathologies are associated with knee damage, such as gout or rheumathoid arthritis, but the primary condition is osteoarthritis (OA). Not only can osteoarthritis cause significant pain, but it also can result in signficant disability as well. Treatment for this condition varies, starting off with oral analgesics and physical therapy to surgical total knee replacmenet. In the gamut of this various treatments, a conservative approach has included intra articular steroid injections. With time, researchers and clinicians determined that other components injected to the knee may additionally provide relief of this condition. In this investigation, we describe different types of knee injections such as platelet-rich plasma (PRP), hyaluronic acid, stem cells, and prolotherapy. Additionally, we describe the role of geniculate knee injections, radiofrequency, and periopheral nerve stimulation. These treatments should be considered for patients with knee pain refractory to conservative therapies.

INTRODUCTION

Although there are many diseases that can damage the joints, osteoarthritis (OA) has been widely regarded as one of the most common diseases that lead to disability and functional impairment in the elderly population, with the knee being the most common joint affected.[1] Other pathologies, such as rheumatoid arthritis and gout, are also causes of chronic knee pain in adults, but OA has a much higher prevalence. OA is a degenerative joint disease mainly characterized by degradation of the articular cartilage and synovial inflammation driven by inflammatory mediators, leading to structural modifications and remodeling of the affected joint.[2] There are many risk factors believed to be associated with the increasing rates of OA in past years, with obesity and physical activity identified as some of the most common culprits for this increase.[3,4]

OA of the knee typically presents with pain around the affected knee joint that can vary greatly in terms of character and severity with decreased range of motion and exacerbation with activity, having the potential to cause significant physical disability leading to a decreased quality of life in affected individuals.[5] OA can be classified as primary or secondary OA, with secondary causes involving those such as trauma, gout, or congenital disorders. OA has been shown to be multifactorial, driven by various inflammatory mediators from both cartilage and bone leading to the inflammation seen in the joint. This is opposed to previous beliefs, that thought that the main driving process was an increased pressure on the joint causing damage.[6]

Treatment options for OA of the knee are targeted at minimizing symptom progression and avoiding the need for invasive surgeries, such as total knee replacements. Widespread research efforts aimed at understanding the pathogenesis of the disease have allowed for advancement in the development of non-operative treatment modalities, thus allowing for more conservative, non-invasive options to slow development and worsening of the disease.

Intra-articular corticosteroid (IAC) injections, possessing an anti-inflammatory effect, have been long regarded

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as the primary treatment modality for pain control in OA of the knee, but opinions on recommendations for their usage have varied. While the positive effects on short term pain relief with IACs has been demonstrated in some analyses, others have shown inconclusive results regarding the effects when compared to placebo.[7,8] Other studies have shown negative outcomes, such as increased meniscal damage, joint space narrowing and thickening, acceleration of disease process, subchondral insufficiency fractures, and osteonecrosis.[9] The widespread uncertainty and efficacy from these studies have promoted increased interest in development and evolution of alternatives for IAC injections, such as prolotherapy, platelet-rich plasma, stem cell, and hyaluronic acid injections.

Intra-articular hyaluronic acid (IAHA) injections have been used as an alternative for IAC injections, but recommendations for its use based on evidence have been controversial. Hyaluronic acid (HA) plays several roles in maintaining the structure of the knee joint, including lubrication and protection from mechanical damage, and is noted to have decreased volumes in joints affected by OA.[10] While some studies have shown use of IACs as superior to IAHA injections for pain relief and function in the first 4 weeks, others showed similar improvement in symptoms when assessed after a 6-month time period.[11,12] An RCT study published in 2006 by *Ozturk Et. Al* analyzed the synergistic effect of use of both IAC and IAHA injections, concluding that combined treatment was superior to the use of IAHA alone.[13]

Further advancement of non-invasive measures for treatment of OA of the knee have led to development of biological treatments to minimize disease progression. Studies analyzing the use of platelet-rich plasma (PRP) have generally shown significant differences in short- and medium-term analgesia of patients with OA of the knee when compared to other modalities. However, lack of standardization across trials and PRP preparations has made it a challenge for this treatment modality to be strongly recommended by any guidelines.[14-16]

The utility of mesenchymal stem cells (MSC) has also been studied as a treatment for OA. Stem cells can differentiate into several different cell types, thus potentially contributing to cell regeneration in the affected joint.[17] Although use of MSC has been shown to provide symptomatic relief and increased functionality of the arthritic knee, several guidelines have recommended against their use due to inconsistent methodologies used across studies.[18,19] The guidelines specifically recommending against their use include those of OARSI and ACR.[11,20] Despite these recommendations, many are optimistic about the potential of MSC therapy, but needs further research involving standardized methods. Although fairly uncommon, prolotherapy is another form of regenerative therapy that can be used to treat OA of the knee. Prolotherapy involves injection of a solution, often dextrose, either intra-articularly, peri-articularly or both, and is believed to trigger an inflammatory response, thus contributing to regeneration in the affected joint.[21,22] The efficacy of prolotherapy has not been extensively studied and this lack of studies has prevented this modality from gaining significant traction, but has gained interest due to the simplicity of its use, relatively cheap cost, and high safety profile.[23] Although fairly few studies have been completed comparing the use of prolotherapy with other modalities, studies comparing it's use to IAHA showed significantly more improvement in the IAHA group, and studies comparing it's use to PRP strongly favored the use of PRP in regards to improvement in pain scores.[24,25] However, a RCT comparing levels of knee pain in the prolotherapy group to physical therapy group showed better pain improvement with prolotherapy, demonstrating that there is some degree of benefit with its use.[26]

With new development and research in advanced treatment modalities—hyaluronic acid, prolotherapy, mesenchymal stem cells, platelet-rich plasma—treatment for OA of the knee has evolved substantially and created many alternatives to the use of corticosteroids. Geniculate injections and radiofrequency ablation, along with peripheral nerve stimulation are also being studied for patients with knee pain and failure from more conservative treatment options.

PRP FOR KNEE INJECTIONS

Platelet-rich plasma (PRP), also known as platelet-rich fibrin (PRF) or platelet-rich growth factors (PRGF), has been frequently used in clinics as a treatment of OA.[27] PRP, one of many orthobiologics—naturally occurring substances in the body—is a minimally invasive treatment with high healing potential.[28] PRP is obtained from a patient's centrifuged blood sample forming a platelet rich product that is subsequently used as injectate. Its mechanism of action involves releasing growth factors and cytokines, diminishing cartilage catabolism, suppressing inflammatory mediators, stimulating cell growth, and alleviating synovial inflammation, which altogether contributes to the overall healing process of OA.[27,29]

There has been an increasing number of clinical trials using PRP as both conservative and intraoperative treatment of knee disorders and surgeries. Trams et al. performed systemic review and the first meta-analysis of the clinical use of PRP in all knee diseases. This study reported several advantages in the use of PRP in OA. PRP was demonstrated to be safe for patients compared to control with no significant difference in the unfavorable outcomes. It also highlighted less pain in short-term follow up and decreased blood loss in the PRP group following TKA.[30] Grassi et al. performed a meta-analysis on six randomized control trials in which time for return to sport after acute muscle injuries was significantly lower in the PRP group.[31] Trams et al. verified this advantage of PRP including hamstring injuries. Current studies of PRP treatment after muscle injuries are promising, yet prospective studies with larger sample sizes and less bias are needed.[30]

Although PRP has these reported benefits, leukocytes in PRP can also increase proinflammatory activity by releasing inflammatory cytokines and markers, which raises concern of possibly aggravating knee OA. Kim et al. explored PRP regarding leukocyte concentration. They showed a sig-

nificant difference in the frequency of adverse reactions after PRP injections between Leukocyte Poor-PRP (LP-PRP) and Leukocyte Rich PRP (LR-PRP).[32] LR-PRP caused more swelling and pain immediately following the injection in the knee, indicating that PRP has an increased risk of exacerbating knee OA depending on the leukocyte concentration.[33] Despite the difference in the incidence of adverse reaction, intra-articular PRP injections including both LP-PRP and LR-PRP showed improvements above the minimal clinically important difference (MCID) with regards to pain and function in knee OA patients.[32]

Moreover, cytokine profiling of PRP performed by Riewruja et al. revealed an increase in cell migration and proliferation of OA chondrocytes, when cultured with PRP compared to fetal bovine serum and platelet-poor plasma (PPP) in vitro.[34,35] They also explored cartilage specific gene expressions such as COL2A1 and SOX9 in order to investigate how PRP affects redifferentiation of OA chondrocytes. COL2A1 and SOX9, both vital parts of cartilage matrix formation, are degraded in knee OA.[36,37] Yet, there was a significant increase in COL2A1 mRNA expression in OA chondrocytes cultured with PRP. PRP treatment seems to have an influence on the expression levels of SOX9 as well as aggrecan, which is a proteoglycan found in cartilage matrix even though there are studies showing contrasting data.[38,39]

To explore the efficacy of different formulations of PRP, Palco et al. compared the potential therapeutic effects of treating OA patients with platelet and leukocyte rich plasma with PRP + HA. PRP + HA treatment, having the anti-inflammatory aspect of PRP combined with viscosupplementation of hyaluronic acid, showed a significantly better outcome in terms of knee mobility and function up to one year. Furthermore, both groups showed comparable improvements in pain and self-reported activity level of OA patients. Yet, further studies are needed to conclude if either formulation is more recommended than PRP alone.[40] Similarly, Zhao et al. reported a better WOMAC Function and Total Scores, VAS ratings for pain (after 6 months of treatment), and Lequesne Index scores in PRP + HA treatment compared to intraarticular injection of PRP alone. There was no significant difference in the incidence of adverse effects between PRP + HA and PRP or HA alone.[41]

Additionally, concentrations of PRP with varying amounts of platelets were investigated. Bansal et al. demonstrated that a PRP formulation with 10 billion platelet counts in a volume of 8ml provides improved chondro-protection and symptoms compared to control in knee OA. They also hypothesized that higher platelet counts causes more release of growth factors, which could potentially lead to a better outcome.[42]

In addition to different formulations, different number of injections and their clinical results were analyzed. A study comparing two and four PRP injections at a 6-week interval in 125 knee OA patients revealed that there were no significant differences in the levels of synovial inflammatory cytokines, anti-inflammatory cytokines, and growth factors at 6 and 18 weeks after the first injection but had similar clinical improvement until 1 year.[43]

Regarding PRP versus other forms of injection, meta-analysis comparing HA and PRP in therapeutic treatments of knee OA showed a better knee function and reduced pain at six and 12 months follow ups.[44,45] There is also evidence showing more benefits of using single intraarticular PRP injection over corticosteroids injection. Furthermore, triple intraarticular PRP injections, separated by a week, had further benefits over single injections of PRP or corticosteroids.[46] However, in contrast to promising results reported from other studies, Bennell et al. reported no significant difference in pain score or change in join structure-medial tibial cartilage volume at 12 months when comparing intraarticular injection of PRP with saline placebo.[47] There are studies that have also compared PRP with other potential cell therapies injections such as bone marrow aspirate concentrate (BMAC). Pain and functionality scores were obtained at baseline and different time points over 12 months after the injection PRP or BMAC. While BMAC produced significantly better VAS, KOOS, and WOMAC scores for 12 months, PRP didn't show any significant improvement in all scores. Additionally, BMAC, in direct comparison to PRP, showed significant improvement in all scores and outcomes.[48]

Despite the promising findings of PRP and other therapeutic injections, the ideal dosage, timing, and frequency of injections were not determined in these studies and must be investigated in the future.

STEM CELLS FOR KNEE INJECTIONS

There have been numerous therapeutic uses of stem cell therapy as a treatment for different diseases. The ability of stem cells to differentiate and regenerate into various cell types and tissues is thought to be effective for degenerative diseases like OA.[49] Mesenchymal stem cells (MSC) specifically have the potential to differentiate into cells of mesodermal lineage such as osteoblasts and chondrocytes, thus they can be utilized in tissue repair and regeneration of OA. However, instead of a direct differentiation into these cells, MSCs modulate the environment in OA through paracrine pathways.[50] Moreover, its mechanism of action involves inhibition of T cell proliferation and monocyte maturation, and expression of anti-inflammatory cytokines, providing anti-inflammatory benefits.[50] MSCs are also involved in the recruitment and stimulation of resident cells, which can ultimately promote repair of OA.[51]

Regarding clinical application, according to Jo et al, a trial of IA injection of MSCs at high dose into knees of OA patients showed improved joint function and pain without causing adverse events. This study also showed decreased cartilage size in the medial femoral and medial tibial condyles by regeneration of hyaline-like articular cartilage.[52] Additionally, a systematic review done by Jevotovsky et al. reported that stem cell treatment could halt cartilage damage and decrease joint damage seen on MRI.[53] Freitag et al. compared the efficacy of intra articular adipose-derived MSC (ADMSC) treatment of either a single injection or two injections (at baseline and 6 months) with control of conservative management in knee OA patients.

They concluded that ADMSC treatment had a significantly better improvement in function and pain than control. Furthermore, they found better stabilization of OA or a halt in cartilage loss in two intra articular ADMSC injections than a single injection. This stabilizing aspect of MSC therapy is consistent with the idea of its effect involving paracrine and other supportive signaling.[50]

In addition to therapeutic efficacy, the safety of MSCs was also investigated due to synovial MSCs obtained from OA patients often having Trisomy 7, which can be associated with tumor formation. Mizuno et al. investigated the safety of the therapeutic use of these MSCs with trisomy 7 in OA patients and discovered that out of 10 patients that they monitored, three of them had 5-10% of their synovial MSCs with trisomy 7. Yet, no abnormalities or adverse events such as tumor formation was found after 5 years follow up in all 10 patients who had MSCs transplantation with or without trisomy 7. They all showed similar results in the safety tests they conducted.[54]

Furthermore, studies investigated the efficacy of MSC injection versus other injections typically used for OA. For example, Kim et al. retrospectively screened for and compared the therapeutic effects of intra-articular injections of MSCs and HA up to 1 year in knee OA patients. In the MSC injection group, significant improvements in VAS, IKDC, and Lysholm scores were consistently seen throughout the entire duration of study. In the HA injection group, there was a significant decrease in VAS pain scores at 1 month, yet an increase at 3 months and 1 year post-injection. The KDC and Lysholm scores improved initially but worsened after 3 months post-injection. At 1 year post-treatment, VAS, IKDC, and Lyshom scores were significantly better in MSC group than in HA group. This strongly suggests that MSC treatment may result in a better clinical outcome long-term, even though HA treatment may show more evident improvement short-term. Nevertheless, a larger sample size with longer studies are needed for validation.[55] Similarly, Lamo-Espinosa et al. conducted a randomized clinical study comparing the effects of HA treatment alone (control) or combined with increasing doses of bone marrow MSCs on 30 knee OA patients. Compared to the control group, bone marrow MSC + HA treatment group had a better VAS score without adverse effects in all follow ups up to 12 months. The high-dose bone marrow MSC group also showed a consistent improvement in WOMAC values, altogether suggesting a better outcome in terms of pain and function. X-ray on control group showed a decrease in knee joint space width, which was not found in high-dose bone marrow MSCs group. MRI on the high-dose group also revealed a small reduction in joint damage.[56]

Additionally, MSCs in combination with other compounds with therapeutic potential were studied. A co-injection of synovial membrane derived MSCs and apigenin 0.3μM into knee OA rats has been reported to reduce the levels of several inflammatory cytokines such as TNF-a, MDA, and IL-1B while increasing the levels of SOD, Sox-9, COL2A1, and aggrecan. Apigenin, as a complementary use, could possibly augment the beneficial effects that MSCs have in OA.[57] A composite of umbilical cord blood-derived MSCs and 4% HA hydrogel has been demonstrated to repair a symptomatic osteochondral knee joint defect. There was a significant improvement in pain and function of knee joint at 12 months post-surgery. MRI showed the knee joint entirely filled with a hyaline-like cartilage that became uniform with the normal cartilage around it. This restoration of cartilage was maintained for 5.5 years.[58]

Lastly, more studies paying attention on technique, regulatory policy, and optimization of differentiation potential of stem cells is needed in order to achieve more consistency and homogeneity in the future.[59]

PROLOTHERAPY FOR KNEE INJECTIONS

Prolotherapy is an evidence-based injection therapy used for chronic painful musculoskeletal conditions, including knee osteoarthritis (OA).[60] This injection technique introduces small amounts of an irritant solution to sites of painful and degenerated tendon insertions, joints, ligaments, and in adjacent joint spaces over many treatment sessions to promote the growth of normal cells and tissues.[61] There is limited understanding regarding the exact mechanism. However, it is thought to involve the initiation of a local inflammatory cascade which leads to tissue proliferation and remodeling.[62]

HYPERTONIC DEXTROSE PROLOTHERAPY (DPT)

Although various injectants may be used, the most common is hypertonic dextrose which has been used since the 1950's and is the most studied. Dextrose is low cost and widely available in the clinical setting. DPT seems to be under-utilized in medicine despite growing evidence of efficacy and effectiveness.[63] Animal studies have reported that peritendinous dextrose injection consistently resulted in fibroblast and vascular proliferation, dense collagen deposition and increase in ligament thickness, energy absorption and ultimate load bearing ability.[63]

A prospective, uncontrolled study on DPT with one year follow up was done in the outpatient setting to determine whether prolotherapy treatment improves pain, stiffness and function in adults with symptomatic knee osteoarthritis (OA) compared to baseline. Primary outcome of the study was the Western Ontario McMaster University Osteoarthritis Index (WOMAC) and the secondary outcome measure was the validated Knee Pain Scale (KPS). The tertiary outcome measure was procedure related pain severity and participant satisfaction. Participants (n=36) received an average of 4.3+/- 0.78 prolotherapy sessions and 22 participants received treatment on both knees. A single intra-articular injection of 6 mL of 25% dextrose was made using an inferomedial approach. Extra- articular injections were done "on bone" at major tendon-tendon and ligament insertions through up to 15 skin punctures using a peppering technique. WOMAC scores showed an overall improvement with prolotherapy compared to baseline ($p<.001$). Overall the study found a significant and consistent improvement in knee pain, function and stiffness at 52 weeks after treatment with prolotherapy. The effect of prolotherapy in the

unaffected knee was also studied. Interestingly, participants reported significant improvement in KPS scores on the uninjected knees, possibly due to decreased compensatory mechanisms.[64]

HYPERTONIC DEXTROSE PROLOTHERAPY (DPT) VS. NORMAL SALINE

Intra- and periarticular dextrose prolotherapy injections have been shown to reduce pain, improve function and quality of life in patients with knee OA compared with blinded saline injections.[60,65] The efficacy of intra-articular hypertonic dextrose prolotherapy (DPT) vs normal saline (NS) injection for knee OA was studied in a single- center, parallel-group, blinded, randomized controlled trial conducted at a university primary care clinic in Hong Kong. The DPT solution comprised of 5 ml of 25% dextrose and the control group received 5 ml injections of normal saline. Injections were administered at 0, 4, 8, and 16 weeks for each study group. The primary outcome was the WOMAC pain score. The secondary outcomes were the WOMAC composite, function and stiffness scores; objective physical function test results; visual analogue scale (VAS) for knee pain, and EuroQol-%D score which measured health-related quality of life. There was statistically significant improvement in the DPT group compared with the NS group on the primary outcome of WOMAC pain score at 52 weeks. WOMAC pain score showed a difference-in-difference estimate of −10.34 (95% CI, −19.20 to −1.49, P = 0.022).[60]

QUALITATIVE ASSESSMENT OF PROLOTHERAPY FOR KNEE OSTEOARTHRITIS

Although there have been more recent studies on the quantitative outcomes of prolotherapy in knee OA, the qualitative assessment of patient experiences after receiving prolotherapy has been less studied.[66] This could be a potential limitation to establishing routine care for knee OA. There is also a lack of familiarity with the procedure and a general fear of injection-based therapy.[66]

Studies have been done to evaluate perceptions and experiences among those who have received prolotherapy for knee OA. Three randomized control trials (RCTs) and two open label studies reported longitudinal improvement in self-reported knee OA outcomes in response to prolotherapy compared with baselines status, blinded placebo control injections and active treatment.[67-69] A majority of participants reported positive results in quality of life. Reduced knee pain and stiffness were reported along with improved function from baseline status. Prolotherapy was also shown to be perceived to be a safe treatment with no long term side effects.[66] All interviewed participants (n=22) would recommend or had already recommended prolotherapy to others. Some participants (n=4) reported little to no change in their symptoms. Overall, most participants in the study experienced a safe, satisfactory and substantial decrease in pain and improved ability to perform daily living throughout the 52 week study period.[66]

HYALURONIC ACID FOR KNEE INJECTIONS

Knee OA is managed by attempting to reduce pain and disability using non pharmacological treatments.[70] First line treatment for mild to moderate knee OA includes education, exercise and treatment such as analgesic or non steroidal anti-inflammatory drugs (NSAIDS). Next line therapy as disease progresses is intraarticular (IA) corticosteroid (CS) injections, but the long-term use of CS is not recommended. Intra-articular hyaluronic acid (HA) injections have been widely used to reduce pain by increased synovial fluid which protects the knee joints. IA HA can reduce pain for several months in comparison to IA CS injections which have immediate but short-lived effects. In addition, HA has been found to delay total knee replacement (TKR) in patients with KOA.[70]

EFFECTIVENESS OF INTRA-ARTICULAR INJECTION OF HYALURONIC ACID

A study evaluating the efficacy of intra-articular injection with HYAJOINT Plus, a bio fermentation derived, high molecular hyaluronic acid, on the structural progression of cartilage in patients with knee OA was conducted using objectively promised ultrasonography (US) evaluation.[71] The primary outcome for structural change of the knee joint was the US findings. The secondary efficacy outcome measure included WOMAC total and subscale scores. Significant US grade improvement changes of cartilage were found between baseline and follow-up visits over the medial femoral condyle and transverse overall evaluation at 3 and 6 month follow ups, and over the lateral femoral condyle, intercondylar notch, and medial longitudinal area at the 6 month follow up. WOMAC score changes from baseline were significant at the 6 month follow up in total score as well as all 3 subscale scores (joint pain, stiffness, and physical function).[71] Additionally, in a review of systematic review 38 randomized control trials (RCTs), intra- articular injections of HA were shown to have resulted in clinical improvement over baseline pain, stiffness and function up to 3-6 months.[72]

The efficacy of high molecular weight HA added to usual care was also studied specifically in the working population as they are often unable to receive total knee arthroplasty (TKA) due to being involved in a physical demanding occupation.[73] The randomized controlled trial of subjects between 18-65 with symptomatic knee OA measured the response to therapy according to OMERACT-OARSI criteria after 52 weeks, which includes pain, knee related function and patient's global assessment (PGA). The study showed that adding intra-articular injections with a HMW-HA derivative to usual care treatment in an everyday clinical setting resulted in statistically significant improvement of pain, function and PGA in these patients.[73]

TYPES OF HYALURONIC ACID PREPARATIONS

The most studied preparation of intraarticular hyaluronic acid (IAHA) is Hylan G-F 20 which has showed consistent results confirming efficacy in placebo-controlled studies.[74]

Head-to-head trials comparing IAHA preparations found high- molecular weight (MW) Hylan G-F 20 to be superior to low MW sodium hyluronate preparations (Hyalgan, Supartz).[75] IA- Hylan G-F 20 scored better in VAS pain score at the 6 month follow up compared to IA- Hyalgan.

When comparing medium versus high MW IAHA (Hylan G-F 20), no statistically significant difference was found between the outcomes.[76]

HYALURONIC ACID (HA) VS PLATELET RICH PLASMA (PRP)

In a meta-analysis consisting of 14 randomized controlled trials (RCTs) involving 1350 patients, it was found that PRP offers clear advantages in the conservative treatment of knee osteoarthritis.[77] Long term VAS, IKDC, and WOMAC (pain/stiffness/physical function/total) scores at each time point were higher in the PRP group than in the HA group. It was shown that treatment with PRP can reduce long term pain and improve knee joint function with no additional risk. PRP is therefore the preferred method most widely used for the conservative treatment of knee osteoarthritis.[77]

Although many systematic studies suggest that intra-articular injection of PRP has shown to relieve pain symptoms and improve knee functions in patients with knee OA, compared to HA, the effects of PRP therapy combined with HA has been less studied.[78,79] A double blind randomized controlled trial with a 5-year follow-up showed that the combination of HA and PRP improved pain and function in patients with chronic symptomatic knee degenerative changes and OA.[80] There may be a synergistic effect with therapies due to their different biological mechanisms that facilitate the activity of signal molecules such as inflammatory molecules, catabolic enzymes, cytokines and growth factors- therefore playing a role in the treatment of knee OA.[81,82] Studies have also shown that there is no significant difference found in the incidence of adverse reactions between usage of PRP, HA, or both, indicating that the combined therapy is just as safe as the monotherapies.[79]

HYALURONIC ACID AND STEM CELL THERAPY

The use of bone marrow mesenchymal stromal cells (BM-MSCs) in combination with hyaluronic acid was evaluated in a randomized clinical trial with 30 patients diagnose with knee OA.[83] The control group received hyaluronic acid (HA) alone, while other groups received it in conjunction with 10 x 10^6 or 100 x 10^6 cultured autologous BM-MSCs. The higher dose group had a significant reduction in the VAS score at 6 months, indicating clinical benefits to combined therapy with high dose BM-MSCs and hyaluronic acid (HA).[83]

ECONOMIC BENEFITS OF HYALURONIC ACID TREATMENT

There is an increased loss of productivity at work secondary to knee OA, therefore treatment with HMW-HA could have economic benefits.[73] In addition, the treatment costs for patients who use intra-articular hyaluronic acid (HA) and/or knee arthroplasty was studied and quantifies the high-cost nature of arthroplasties.[84] The total cost of treating OA patients during the study period of 5 years was $6.6 billion or $4210 per patient. The majority (61.5%) of the cost was due to primary knee arthroplasty although the majority of the patients (91.2%) did not undergo arthroplasty.[84] Post operative costs made up another 11.6% of the total costs. Non- arthroplasty therapies accounted for about one third of total coses (38.5%) in younger patients with HA accounting for only 3.0 % of the costs.[84]

SERUM HYALURONIC ACID (SHA) AS A DIAGNOSTIC METHOD FOR OSTEOARTHRITIS

Osteoarthritis (OA) should be diagnosed and treated early for the best possible prognosis. Unfortunately, the current diagnostic tools are inadequate.[85] Plain radiography has been the gold standard method of diagnosis, but the sensitivity and specificity of the technique is under question.[86] Magnetic resonance imaging is costly, time consuming and contraindicated in some patients. A potentially useful alternative diagnostic method is the use of serum biomarkers to objectively evaluate disease activity. Hyaluronic acid is one most promising of the several serum biomarkers that are known to be correlated with the extent of OA on radiography of the knee. Previous studies have also reported that serum hyaluronic acid (sHA) concentration is also useful for identifying disease duration, severity, and the extent of knee osteoarthritis pain.[85] It is thought that the concentration of sHA reflects the extent of synovitis which is present at the onset of OA and accelerates disease progression by producing proteases and cytokines.[87,88]

In a 5-year prospective cohort study, the relationship between sHA concentration and radiographic changes in the knee was determined.[85] The knee osteoarthritis computer aided diagnosis (KOACAD) system was used to measure joint space narrowing (JSN) and osteophyte formation. The knees were grouped according to the Kellgren Lawrence (KL) grade. The study found that sHA concentration at baseline was positively correlated with the development or progression of KL grade. Interestingly, sHA concentration at baseline was correlated with JSN in both normal and severely osteoarthritic knees, as assessed by radiograph. This suggests that sHA concentration reflects not only the severity but the likelihood of disease progression in knee OA. A sHA cutoff value of 51.9 ng/mL was predictive of OA progression.[85] It is recommended this value be used during screening for abnormal knee conditions or as an additional evaluation for the risk of OA progression in combination with imaging methods. Overall, the results of the study suggest that an increased sHA concentration can be used to predict knee OA progression.[85]

NEW VISTAS

Geniculate nerves are sensory branches from the femoral, obturator and sciatic nerves, which innervate the knee joint. In general, there are three nerves that are targeted

either in the acute setting postoperatively or for chronic knee pain.[89] These nerves are superolateral, superiomedial, and inferiomedial geniculate nerves. Ultrasound and fluoroscopic landmarks primarily include the osteomuscular planes of the metaphysis.[90]

Patients with chronic knee pain who have benefit are considered for radiofrequency ablation of these sensory nerves.[91] Ultrasound landmarks are limited and most of these geniculate nerve injections are performed utilizing fluoroscopic guidance in chronic pain management.[89,90]

Peripheral nerve stimulation is another technology that includes placement of leads first in a trial and with success, permanent leads are placed for long-term benefit.[92-94] Studies are ongoing with various brands to demonstrate long-term efficacy. Nerve stimulation can be used to target specific nerves to provide symptomatic improvement. This therapy is based on Gate Control Theory which utilizes stimulation of non-nociceptive receptors and inversely inhibits nociceptive stimulation.[89]

CONCLUSIONS

In summary, the knee is the most prevalent joint that causes morbidity in the adult population, which often results in pain and disability. Of the many causes, osteoarthritis is the number one pathology that affects the knee. The most aggressive treatment is surgical knee replacement, but this therapeutic modality is not without its pitfalls and many times poses a high risk to the elderly with many comorbidities. Steroid knee injections have provided pain relief and at times, prolong the course of time before surgery becomes inevitable. Over time, alternatives to steroids have been implemented, such as PRP, stem cells, prolotherapy and hyaluronic acid. Geniculate injections and radiofrequency are commonly employed when injections are unsuccessful. Peripheral nerve stimulation has great potential however, only a subset of patients has shown interest in this technology at present. Hopefully with more studies, practitioners will have an ample variety of different knee injections to treat patients with this disease.

CONFLICT OF INTEREST

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