Level V Evidence

Injections for Knee Osteoarthritis: Corticosteroids, Viscosupplementation, Platelet-Rich Plasma, and Autologous Stem Cells

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Abstract: This article reviews the benefits of corticosteroid, viscosupplementation, platelet-rich plasma, and autologous mesenchymal stem cell injections for the treatment of patients with knee osteoarthritis. Integrating injections into both clinical and surgical practices is complicated given existing health insurance reimbursement policies. This review describes the outcomes associated with these interventions and appropriate methods of navigating the existing reimbursement pathways to help providers implement these treatments into their practices.

Osteoarthritis (OA) of the knee is a degenerative condition that affects 38% to 47% of the population aged older than 60 years.[1] OA exacts a significant economic burden on the American health care system. The estimated annual cost of OA per patient is $5,700,[2] and in 2004 alone, the cost of total knee arthroplasty (TKA) to treat OA was $14.6 billion in the United States.[3] OA has an even greater impact on patient function; it is 1 of the top 5 causes of disability in the United States[4] and is associated with an increase in morbidity and mortality rates.[5] Men and women with OA have difficulty finding work and performing activities of daily living and have an increased mortality rate due to cardiovascular disease and dementia.[4]

Although its pathophysiology is not fully understood, OA is defined by irreversible, progressive damage to the articular cartilage of the knee. There are modifiable and nonmodifiable risk factors. Nonmodifiable risk factors include age, race, sex, and potential genetic susceptibility,[6,7] whereas the key modifiable risk factors include patient weight and activity level.[6,8] The rate of obesity—defined as a body mass index over 30—continues to rise in the United States, and in a 2012 census, 35% of adults, 57% of black women, and nearly 17% of persons aged younger than 19 years were obese.[9]

Current treatment for OA focuses on relieving symptoms and improving function, and it usually begins with patient education on modifiable risk factors, physical therapy, and oral nonsteroidal anti-inflammatory drugs. Patients who remain unresponsive to these treatments may be indicated for knee injections before being indicated for joint replacement surgery. Today, there are 4 main injection therapies: corticosteroids, hyaluronic acid (HA), platelet-rich plasma (PRP), and autologous mesenchymal stem

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cells (MSCs).[10-16] This article reviews the existing literature evaluating the efficacy of injection therapies in the treatment of knee OA through December 2017.

Injection Therapies

Corticosteroids

Corticosteroids have been used for over 50 years with varying degrees of success (Table 1).[17] The pathophysiology of corticosteroids is more understood than that of most other injectable materials, because corticosteroids alter B- and T-cell immune function and inhibit phospholipase A2 to decrease expression of inflammatory cytokines.[18] There is also evidence to suggest that cortisone increases fluid viscosity and HA concentration within the joint space, which theoretically may help to treat OA.[17,19]

Synthetic corticosteroids have more anti-inflammatory potency than does native cortisol, and they are derivatives of prednisolone, an analogue of human cortisol.[20] Depo-Medrol (Pfizer, New York, NY) is the injectable formulation of methylprednisolone acetate, and the fluorinated derivatives of prednisolone are betamethasone, dexamethasone, and triamcinolone. Triamcinolone (Kenalog; Bristol-Myers Squibb, New York, NY) is frequently used as an injectable for orthopaedic conditions. Methylprednisolone and triamcinolone are the 2 most common injectables used for knee OA. They are equivalent in potency, but triamcinolone is less water-soluble,[20] potentially making it a better alternative for patients with diabetes who are at risk of hyperglycemic spurts after injection. Both preparations contain esters, which require hydrolysis by cellular esterases to release the active moiety and last longer than non-ester preparations.[21] The average duration of benefit ranges from 8 to 56 days for methylprednisolone and 14 to 66 days for triamcinolone.[22-24]

Corticosteroids for knee OA are almost always administered with local anesthetics. Lidocaine has a rapid onset of action (2-5 minutes) and a duration of 2 or 3 hours, depending on the inclusion of epinephrine.[25] Because its anesthetic effect wears off so quickly, clinicians frequently add bupivacaine, which has a slower onset (5-10 minutes) but a longer duration of action (4-8 hours).[25] Some clinicians prefer to administer corticosteroid and anesthetics using separate syringes, but Benzon et al.[26] have shown that corticosteroid crystals do not change in aggregation or particle size when mixed with local anesthetics. Previous work has shown that continuous infusion of intra-articular anesthetics may lead to chondrolysis,[27] but no studies have shown similar long-lasting damage from single injections of physiological doses.[28]

When pain relief is achieved from a corticosteroid injection, the benefit is usually transient, lasting anywhere from 1 week to 24 months.[17,29,30] Some clinicians believe that increased symptoms at baseline and the presence of an effusion or synovitis improve the likelihood of response to cortisone injections.[20,31] At least 2 studies have suggested that milder OA is a predictor of a positive response,[32,33] but neither study specified whether Kellgren-Lawrence grades were assessed on posteroanterior flexion (Rosenberg) views, which have been shown to be more sensitive for detecting knee OA.[34] Previous research has suggested that different radiographic views may upgrade the diagnosed severity of OA.[15] Therefore, it is important that future trials comparing the severity of knee OA with injection response specify which radiographic views are used as a correlate to clinical outcomes.

Clinicians should always warn patients that post-injection flares may develop in 2% to 25% of patients within a few hours of injection.[23,35] These flares may last 2 to 3 days but do not predict a poor overall response to therapy.[23] Soft-tissue adverse effects are rare and include skin depigmentation, cutaneous atrophy, and fat necrosis.[20] Systemic inhibition of the hypothalamus-pituitary-adrenal axis was shown to last up to 2 weeks in 7 of 10 athletes after intra-articular injection.[36] The clinical ramifications of this are most likely negligible, but patients may be cautioned to avoid severe physical stress within 2 weeks of injection. Finally, although there is basic-science evidence that increased numbers of corticosteroid injections may lead to cartilage breakdown,[37] the clinical risk of cartilage loss after multiple injections is still very low, at 0.7% to 3.0%.[38,39] One study found that intra-articular triamcinolone may result in significantly greater cartilage loss and no significant difference in knee pain compared with intra-articular saline solution administration.[40] However, this study reported relatively low amounts of cartilage volume loss and a dosing frequency that is greater than most clinicians would provide. In addition, patients included in this study had relatively advanced disease at baseline. Furthermore, most clinicians would stop administering intra-articular injections in the absence of efficacy. After thorough consideration of the literature as of 2013, the American Academy of Orthopaedic Surgeons (AAOS) stated that there is inconclusive evidence to recommend for or against the use of intra-articular corticosteroids to treat knee OA.[41] Despite this, physicians continue to liberally use intra-articular corticosteroids to treat patients with symptomatic knee OA.

Senior Author's Clinical Recommendations. In the senior author's (B.J.C.) practice, corticosteroid injections are commonly used as the initial first-line treatment for symptomatic knee OA. We typically use a single injection consisting of 1 mL of methylprednisolone (40 mg) and 9 mL of 1% lidocaine because we find the volume is well tolerated and patients have rapid