AOTH

Review

Intrarticular injections: when and with what substances?

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Abstract

Intra-articular injections are frequently used as treatment option in primary care clinics for the management of pain in patients with arthritis. However, it is unclear the optimal effect of intra-articular injections for the various types of arthritis. Therefore, we performed this review article to present the available intra-articular injections for arthritis and to discuss their short and long term effect in these patients.

Keywords

Intra-articular injections; arthritis; osteoarthritis; cortisone; hyaluronic acid.

Intra-articular injections are frequently utilized as treatment option in primary care clinics for arthritis and particularly osteoarthritis (OA) of the knee. Over the past three decades, treatments which have been developed for OA aim to reduce inflammation and pain, enhance functionality, prevent joint damage, and slowdown the disease progression. In cases when symptomatic treatment of OA with pharmacologic and nonpharmacologic agents is ineffective in managing pain and dysfunction, we proceed to surgical joint replacement. Until that point, provided early diagnosis and therapeutic intervention have already taken place, we can make an effort to alleviate symptoms and improve the overall quality

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of life for patients.

Depending on patient's medical history, clinical examination and laboratory tests, recommendations may include weight and strain control, exercise as well as the use of analgetics, such as paracetamol, mild opioids and particularly non-steroidal anti-inflammatory drugs (NSAIDs), locally or systemically. In addition, medications for chronic pain are recommended, such as duloxetine and pregabalin. In cases where the disease progresses, intra-articular corticosteroids can be administered. However, it should be noted that corticosteroids are not recommended as a long-term treatment strategy, as their benefits are short-lived and they may have negative effects in patients with comorbidities, like hypertension and diabetes mellitus. Over the last decades, alternative treatments have also been used such as injections of hyaluronic acid, autologous platelet-rich plasma, and stem cells in order to relieve symptoms and delay the need for total arthroplasty.

In the treatment of acute inflammatory, crystal or autoimmune, arthritis and OA flare-ups, intra-articular cortisone injections (betamethasone, triamcinolone, dexamethasone) are beneficial in pain control. However, although concerns have existed regarding their potential to accelerate joint wear over time, there is a theoretical possibility that these injections could slow down the rate of cartilage loss and other structural manifestations of osteoarthritis, because suppressing inflammation could moderate its catabolic effects and minimize joint damage.

Administering injection of cortisone into a joint with synovitis, with the option to repeat the procedure after 4-6 weeks (within a limit of 3-4 per year) does not appear to harm the articular cartilage. In fact, it reduces the inflammation for a duration of at least 2- 4 weeks up to 2-3 months. Therefore it helps to restrict the potential damage that can be caused by its extension, while also allowing other treatments to take effect, such as non-pharmacological interventions like physical therapy.[7]

Hyaluronic acid (HA), a structural molecule of articular cartilage, is the main component of synovial fluid and serves multiple functions such as a lubrication, shock absorption and modification of the inflammatory response. Also, it protects the articular cartilage and maintains joint functionality. However, as individuals age or due to various external factors, the production and molecular weight of HA decrease. Consequently, the joint is not adequately protected, leading to degenerative changes and development of OA. The administration of HA intra-articular (known as viscosupplementation) can be considered as a replacement therapy. It mechanically and biologically supports the joint, providing long-lasting effects by stimulating the secretory cells of the synovial membrane to produce new HA beyond the drug's normal half-life.[2]

The potential benefits include mild inflammation control, improved lubrication, enhanced biomechanics, promotion of cell proliferation, differentiation, migration, and increased protein biosynthesis and secretion[6]. The utilization of HA injections is prevalent in the treatment of OA, especially of the knees, expecting improvement in pain relief and enhanced mobility over the next 1-6 months, particularly when repeated injections are administered on a 2-5 weekly basis. Despite the significant market demand for these injections, their effectiveness is still in question. As a result, many scientific companies opt not to include them in their recommendations.

There is a variety of HA products that differ in formulation, molecular weight, rheological characteristics and concentration. Certain formulations are considered more suitable for specific joints and patient populations, e.g. athletes[1]. As a result, HAs have been developed, with high and low molecular weight, synergistic complexes, such as HA plus chondroitin and other structural components of the joint, that more closely resemble the normal composition of synovial fluid. However, currently there is lack of clinical evidence to support their widely application in our daily practice. HAs of high molecular weight (one shot) are recommended at less frequent intervals but have not demonstrated long-term superior clinical benefit than those with 1,000,000 D. However, they may be more convenient for the patients. Sometimes HAs, particularly those with higher molecular weight, can cause temporary synovitis with pain and stiffness that lasts a few days.

Further research is necessary to acquire a compre-

hensive understanding of the factors that contribute to the repair of musculoskeletal tissue, despite the increasing number of new HA derivatives for the treatment of orthopedic conditions. Regarding symptomatic OA, intra-articular injection of polyacrylamide hydrogel has also been explored as a treatment, yielding positive clinical results[5].

The treatment with autologous plasma rich in platelets (PRP) falls under the category of Orthobiologics that help the body deal with its own injuries and repair itself[4]. It is a fact that platelets are blood cells that participate in blood clotting. PRP is essentially a concentrate of cells, growth factors and inflammatory mediators. This concentrate possess anabolic and anti-inflammatory properties, providing the ability to repair damaged soft tissues and articular cartilage, promote healing, prevent degeneration, reduce pain and accelerate functional recovery. Additionally, PRP stimulates the differentiation of stem cells into the specific tissue type affected by the disease and can also act as a scaffold by utilizing the ability of fibrinogen to form meshes and fill in damaged areas, contributing to normal regeneration and healing. Its analgesic effect is achieved by controlling both the inflammatory reaction and the activation of receptor 4 in nociceptor neurons by proteases. It is utilized in the treatment of acute and chronic musculoskeletal conditions, providing relief from acute and chronic pain and improving functionality in soft tissue diseases such as muscle strains, ligament injuries, tendinopathy, skin lesions and periodontal diseases. Additionally, PRP is beneficial in repair of articular cartilage damage, prevents degeneration and minimizes pain, and is used to address cartilage deficits and early-stage OA.[9]

Platelets continue to produce and secrete growth factors for approximately the initial 7 days. After this period their role is continued by macrophages. That is the reason why the procedure can be repeated after a week, whereas depending on the severity of the condition, 1-5 injections can be administered. The selection of one of the 4 concentrations depends on the specific condition and whether leukocytes and fibrin are included (P-PRP, L-PRP, P-PRF; L-PRF). In OA the recommended administration includes 3 injections. Typically, the second is administered within a week after the first and the third 2-3 weeks later. In case of damages, such as e.g. defects of skin, gums, or other mucous membranes, a gel form can be placed, immediately after centrifugation, without the use of special anticoagulant or after being placed on a special scaffold.

As the use of PRP expands, more scientific challenges will arise. Since our aim is to maximize its effectiveness, our therapeutic strategy ought to be based as much as possible on the pathophysiological condition of the particular disease we are dealing with each time. For example, the role of white blood cells in the concentrate is significant because their participation has the ability to delay healing, e.g in tendon cells, as it causes catabolic and inflammatory effects. On the other hand, if PRP without white blood cells is utilized in acute injuries, due to its strong anabolic effect, it can cause a larger scar, which is something we want to avoid. In recent injuries, the use of L-PRP (leukocyte) and in subacute P-PRP (pure) appears to be more beneficial.

Similarly, comprehensive understanding of the role of each growth factor (GF) is necessary in order to make our treatment more targeted so that the most beneficial components of PRP would be used in the right place and at the right time. Some GFs may be beneficial in certain applications and harmful in others. For example, TGF-β can promote the process of fibrosis, can be useful in the healing of ligaments and tendons, but can hinder the healing of muscle sprain. Vascular endothelial growth factor (VEGF) aids vasculogenesis and muscle regeneration, but may be detrimental to articular cartilage healing. Moreover, cytokines may act through conflicting pathophysiological pathways. Therefore, it is important to accurately assess the evolving microenvironment of the particular condition at the crucial point in order to achieve effective treatment.

The main recommendations for intra-articular PRP injections which were presented by the European League against Rheumatism (EULAR) are the following: an effective treatment regarding early or moderately symptomatic OA includes PRP injections. However, they also may be beneficial in severe OA. They are suggested as second option in case the usual symptomatic treatment does not have

the desired results. They should not be applied during OA flare -ups with significant fluid build-up. Treatment may include 1 to 3 consecutive injections. P-PRP (leukocyte poor) should be preferred and should not be mixed with injectable anesthetic or corticosteroid.

In recent years, the role of stem cells (MSCs: Mesenchymal Stem Cells) has become more significant, particularly in regenerative medicine and the treatment of OA, especially of the knee and hip. The fact that they are present throughout the whole body is indicative of their significant role in tissue repair and regeneration[8]. Their ability to migrate to injured areas, to inhibit pro-inflammatory pathophysiological pathways, to promote tissue repair through the release of anabolic cytokines in combination with their direct differentiation into specialized cartilage and bone cells, enhance their immunomodulatory and anti-inflammatory properties and consequently their potential in treatment of OA.[10]

It is an easy procedure to collect stem cells from various tissues such as bone marrow, adipose tissue, synovial membrane and amniotic fluid and directly inject them into the lesion area without the need for the patient to be hospitalized.

Local anesthetics should be administered intra-articular sparingly, because there is a possibility to cause chondrolysis, particularly when co-administered with steroids.[3] In daily clinical practice, injections into superficial and large joints such as the knee, shoulder and ankle are performed through specific access points. On the other hand, in cases of deep ones such as the hip and facet joints of the spine, ultrasound guidance or other imaging method may be utilized. The injection in small joints is sometimes not easy, especially in cases of obvious degenerative changes. Injections with local anesthetic, combined or not with steroid, can also be administered peri-articularly in serous bursae, tendon sheaths and ganglion cysts in order to relieve inflammation and pain, as well as other soft tissues such as in the trigger points of muscle aponeurosis and around nerves. Dry needling, meaning injection without medication, has also appeared beneficial regarding tendon healing and trigger point release. In addition, trials have been conducted regarding co-administration of steroid and HA, as well as HA and PRP.

In conclusion, in a chronic disease such as OA, the appropriate treatment option is critical for each individual patient. Current literature in combination with our experience indicate that intra-articular injections are safe, with minimal side effects, such as arthralgia and edema, and in even more rare occasions infection, and have positive results in terms of patient satisfaction.

Intra-articular administration of corticoids has short-term results, but is considered the best option in treating OA flare-up with hydrarthrosis that persists despite the use of NSAIDs. In this particular case, the result can be evident due to the remission of inflammation and hydrarthosis. Regarding the effectiveness of the other injections, because of the fact that we rely mainly on the patients' reports, we cannot be certain whether this result is due to the modification of the disease or the placebo effect. However, PRP and stem cells seem to work better in patients under 60 with mild OA. In cases of older patients or those with more advanced OA who do not wish to undergo surgery, a better option seems to be the administration of HA or a combination. Especially in knee OA and other supporting joints, PRP and stem cells are preferred in patients with a body mass index <30, while HA administration is more common in overweight patients or those with axial disorders.

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