Intra-Articular Corticosteroid and Hyaluronic Acid Injections in the Management of Osteoarthritis

Osteoartrit Tedavisinde İntraartiküler Kortikosteroid ve Hyaluronik Asit Enjeksiyonları

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Summary

Intra-articular corticosteroid injections have long been used to treat osteoarthritis, whereas intra-articular hyaluronic acid injections for only a few years. In the literature, evidence-based reports on the efficacy of these compounds are non-existent. In the presence of acute hydrops in an osteoarthritic knee an intra-articular corticosteroid injection following aspiration of the joint can be considered. A maximum of 3 injections can be administered at intervals of 8 to 10 days, to be repeated every 6 months if absolutely necessary. A patient with a dry and painful osteoarthritic knee can be a candidate for intra-articular hyaluronic acid injections at weekly intervals, every 6 months if need be. There is a need for a clear consensus about the management of monoarthritis consequent upon osteoarthritis. In the present paper a practical approach is proposed, based on the available literature. *Turk J Phys Med Rehab 2005;51(3):79-82*

Key Words: Intra-articular corticosteroids, intra-articular hyaluronic acid, osteoarthritis

Özet

Eklem içi kortikosteroid enjeksiyonları osteoartrit tedavisinde uzun süreden beri kullanılmaktadır. Oysa eklem içi hyaluronik asit injeksiyonları sadece son yıllarda kullanılır hale gelmiştir. Literatürde bu ajanların etkinliği açısından kanıta dayalı raporlar bulunmamaktadır. Osteoartritli bir dizde akut efüzyon varlığında eklemden aspirasyonu takiben eklem içi kortikosteroid uygulaması düşünülebilir. 8-10 günlük aralar ile en fazla 3 enjeksiyon uygulanabilir ve eğer çok gerekli ise her 6 ayda bir tekrarlanabilir. Kuru ve ağrılı bir diz ise haftalık aralar ile uygulanan eklem içi hyaluronik asit enjeksiyonu için aday olabilir. Gereksinime göre uygulamalar 6 ayda bir tekrarlanır. Osteoartrite bağlı olarak gelişen monoartritlerin tedavisinde açık bir konsensuse ihtiyaç vardır. Bu yazıda mevcut literatür ışığında pratik bir yaklaşım önerisinde bulunulmaktadır. *Türk Fiz Tıp Rehab Derg 2005;51(3):79-82*

Anahtar Kelimeler: İntraartiküler kortikosteroidler, intraartiküler hyaluronik asit, osteoartrit

Introduction

Intra-articular (IA) corticosteroid injections have long been used to treat osteoarthritis, whereas IA hyaluronic acid injections for only a few years. Unfortunately, in the literature, evidence-based reports on the efficacy of these compounds are non-existent. There is a need for a clear consensus about the management of monoarthritis consequent upon osteoarthritis.

In the present paper a practical approach is proposed, based on the available literature.

1. Intra-Articular Corticosteroid Injections

Already in 1930 IA injections were used for the treatment of osteoarthritis in order to directly address cartilage damage and synovial membrane inflammation. In this way an attempt was made to alleviate the complaints and halt the progression of the disease. IA corticosteroids were frequently administered for the symptomatic treatment of peripheral joint osteoarthritis. Most of the studies deal with osteoarthritis of the knee. This also applies to the evidence-based literature.

Different forms of IA corticosteroids exist, based on the chemical structure and solubility. Hydrocortisone is the most physiological of all available corticosteroids. Prednisolone is less soluble. The addition of a methyl group to obtain methylprednisolone diminishes the solubility to some extent and may prolong the duration of effectiveness. The introduction of a fluoro atom increases the pharmacological activity. It can be postulated that the more complex the molecule, the less soluble and the longer it is retained in the joint. Fluoridated molecules have the strongest

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action (1). Nevertheless, IA corticosteroids do not remain in place for a long time. A systemic effect is also present. The depression of endogenous plasma cortisol after an IA corticosteroid injection may last three to four weeks (2). The anti-inflammatory action of each product in relation to an equivalent dose must also be taken into account. The anti-inflammatory effect of betamethasone and dexamethasone is 20 to 25 times greater than that of hydrocortisone. The most commonly available 1 ml vials contain an equivalent dose. The short-acting water-soluble forms are rapidly absorbed into the blood stream and consequently have more systemic effects. The long-acting crystalline depot preparations slowly release the corticosteroid and have less systemic effects. Mixed preparations also exist. The injected dose usually depends on the size of the joint. For the knee, ankle or shoulder joint 1 ml vial is sufficient, for a medium-size joint (wrist) half of a vial, and for smaller a quarter of a vial is adequate.

IA corticosteroids are administered to reduce local inflammation. The principal effect of glucocorticoids is the increased production of certain proteins, mainly lipocortin. Its anti-inflammatory action is based on the inhibition of phospholipase A2, which converts membrane phospholipids into arachidonic acid with a subsequent intracellular production of prostaglandins, leukotrienes and oxygen radicals (3). Stimulation of lipocortin production inhibits the pro-inflammatory cytokine production, including interleukin-1, interleukin-2, interferon-α, tumor necrosis factor, etc. (4). Glucocorticoids inhibit the synthesis of pro-inflammatory enzymes, like collagenase, elastase and plasminogen activator (5).

Indications and contra-indications

IA corticosteroid injections are frequently used to treat a flare of osteoarthritis with hydrops, or posttraumatic synovitis. Other indications include early retractile capsulitis of the shoulder, rheumatoid arthritis, and even crystal monosynovitis, although corticosteroids are definitely not the first choice for this last condition.

General contra-indications for IA corticosteroids are local or generalized infection, immune deficiency, coagulation disorders, prostheses and a pregnancy of less than 16 weeks. Relative contra-indications are diabetes and a pregnancy of more than 16 weeks.

Side effects

IA corticosteroid injections may have a number of side effects, of which facial flushing is the most common (up to 40%). It is benign, self-limiting, and disappears within 24 to 48 hours, but the patient should be informed of its possible occurrence. Facial flushing also depends on which product is used and is more frequent with triamcinolone preparations. Van der Windt et al. compared the effectiveness of IA corticosteroid injections with physiotherapy for the treatment of frozen shoulder. With corticosteroids flushing occurred in 17% of cases, whereas in only 2% of cases treated with physiotherapy.

After IA injections, mainly with hydrocortisone-acetate and less with an acetonide ester or triamcinolone hexacetonide, chemical synovitis, mostly acute but self-limiting, develops in 2 to 5% of cases. Pain and swelling may already occur after 6 hours and subside within 12 to 48 hours. Chemical synovitis or "postinjection flare" is a corticosteroid crystal-induced synovitis. Steroid arthropathy is a controversial subject, but the risk is low if the number of injections is small. An accelerated deterioration of weightbearing joints is, however, difficult to distinguish from the normal or natural course of osteoarthritis. Prevention is thus very important and repeated injections must be avoided. The standard is a maximum of two to three injections per year.

Septic arthritis is rather uncommon thanks to sterile material, meticulous skin disinfection and judicious use.

A variety of systemic effects can occur. In the musculoskeletal system these include muscle weakness and atrophy, steroid myopathy, avascular necrosis, and osteoporosis. Gastrointestinal systemic effects are peptic ulcer, abdominal distension and pancreatitis. Fluid and electrolyte disturbances have also been described and are characterized by sodium retention, potassium depletion, hypokalemic alkalosis and hypertension. Endocrinological systemic effects include irregular menses, Cushing syndrome, reactivation of latent diabetes, dysregulation of diabetes mellitus, and growth inhibition. Dermatologically, delayed wound healing, skin atrophy, petechiae and ecchymoses, striae, hirsutism, hyperpigmentation and acne are observed. The ophtalmological effects include glaucoma, exophtalmia and posterior subcapsular cataract. Corticosteroids can also mask an infection or activate a latent infection and diminish the resistance to mycobacteria, Candida albicans, tuberculosis and viruses.

Evaluation of the literature data

Papers on the use of IA corticosteroids for osteoarthritis are mainly confined to the knee. Corticosteroid injections for rheumatoid arthritis or juvenile rheumatoid arthritis, and facet joint injections are beyond the scope of this review.

In a systematic review paper on IA corticosteroids for osteoarthritis of the knee, a minor advantage and pain reduction lasting from one week to one month, were found compared to placebo (6).

In a randomized clinical trial (7) 89 patients with osteoarthritis of the knee underwent joint aspiration followed by a steroid injection, with a beneficial effect on pain and functional index in the short term (four weeks).

In a more recent meta-analysis (8) corticosteroids were found to have a positive effect on the symptoms for two weeks. The dose was equivalent to 6.25 to 80 mg prednisolone. The effect also remained positive in the long term. A significant symptomatic improvement was obtained after 16 to 24 weeks with a dose equivalent to 50 mg prednisolone.

The authors mentioned a possible positive effect of publication bias.

In two systematic review papers (9,10) the use of IA corticosteroid injections for shoulder pain was evaluated. Compared to placebo, no advantage with respect to pain reduction and improvement of the range of motion was found. In a randomized clinical trial Snels (11) et al. treated 37 patients with three IA triamcinolone injections and compared the effects with placebo (saline solution). No significant difference in pain score or change in range of motion or function was observed.

Studies (10) have also been conducted on the use of corticosteroids combined with lidocaine or not. In a systematic review paper no significant difference was demonstrated between IA corticosteroids combined with lidocaine and lidocaine alone in 48 patients with frozen shoulder. The assessment of the results was based on the pain score and the range of motion. A randomized study, in which corticosteroids (methylprednisone acetate) or placebo was injected intra-articularly following an arthroscopy for a synovial biopsy or for documenting the diagnosis of osteoarthritis, showed no clear differences in the Western Ontario Mc Master (WOMAC) score or Lequesne index at 8, 12 and 24 weeks. After 4 weeks the IA corticosteroid scored better in the evaluation of the Osteoarthritis Research Society International (OARSI) criteria (12). The dose required to improve symptoms has also been studied (13). In a randomized clinical trial of 57 patients with frozen shoulder, a comparison was made between 40 mg and 10 mg triamcinolone. After six weeks markedly greater

relief was obtained with the higher dose, as measured by means of the VAS pain score, improvement in range of motion and functional improvement, but the difference disappeared after six months.

High-quality studies on the use of IA corticosteroids for shoulder disorders are scarce. Moreover, the clinical outcome is correlated with the accuracy of the injection. Even in experienced hands 10% of the injections would not have been given correctly.

Consequently it has been suggested that the injections be administered under fluoroscopic or ultrasonographic guidance.

The studies showed that diabetic patients who had received corticosteroids, required a higher dose of insulin or peroral antidiabetic drugs. The combination with non-steroidal anti-inflammatory drugs increased the risk of gastric bleeding. Barbiturates, phenylbutazone and phenytoin diminished the effectiveness of the corticosteroids.

2. Intra-Articular Hyaluronic Acid Injections

These so-called chondroprotective drugs, developed to inhibit cartilage degeneration, are controversial. Previously, glucosamine derivatives were used. More recently, IA hyaluronic acid has been introduced to treat osteoarthritis. Hyaluronic acid is a high-molecular weight polysaccharide and a major constituent of synovial fluid and cartilage.

In osteoarthritis the molecular weight and concentration of hyaluronic acid are decreased. According to the concept of viscosupplementation IA hyaluronic acid would be beneficial in restoring the viscoelasticity of synovial fluid. It also has a number of biological actions. In preliminary studies on the use of IA hyaluronic acid injections, it was postulated that these would protect the articular surface and hence alleviate the pain and improve the range of motion. This would allow to reduce the use of non-steroidal anti-inflammatory drugs. Several products are available in Belgium. Largely, a distinction is made between low-molecular weight and high-molecular weight hyaluronic acid. Most injections are given for knee osteoarthritis. In 1998 more than 10 million viscosupplementation injections were administered in the USA, with local reactions in only 3% of cases. During the same period 16,500 patients died of side effects of anti-inflammatory drugs for osteoarthritis. No anaphylactic or generalized side effects of IA hyaluronic acid injections have been reported. Adverse reactions have been reduced even more by the introduction of the new generation of biotechnologically produced hyaluronic acid products.

The efficacy of hyaluronic acid is less as the cartilage becomes thinner. An acute infection must be treated first.

The evidence-based literature mainly includes studies on knee osteoarthritis. Many contradictory data have been reported.

A first state-of the-art review on the use of viscosupplementation in the last 2 decades, was published by Peyron (14) in 1993. Pain relief was achieved, lasting from some weeks to as long as 6 months. A positive response was obtained in 65 to 80% of cases. Compared to studies in which corticosteroids were used, the beneficial effect lasted significantly longer. Tolerance was generally very good. In 2003 a systematic review was published by Espallargues and Pons (15), who reported a predominantly short-term effect of a course of hyaluronic acid injections (Hylan-G-F 20) on the symptoms and knee function. Furthermore, hyaluronic acid delayed the need for knee replacement. Some trials have also shown long-term benefits. In a randomized clinical trial (16) IA hyaluronic acid was compared with placebo and with oral naproxen. One injection was administered every five weeks. The follow-up at 26 weeks showed significant pain reduction during walking and at rest, compared to placebo. The improvement in the range of motion was at least as effective as after 26 weeks of continuous naproxen therapy, with less side effects. In a second randomized clinical trial (17) hyaluronic acid was compared with placebo in 110 patients who received 1 injection every 5 weeks for 26 weeks. No significant difference in pain was observed. In a double-blind (18) randomized multicenter study of patients with mild to moderate knee osteoarthritis, 5 IA hyaluronic acid injections were administered at one-week intervals and compared with placebo (saline solution). The WOMAC scale was used to assess the results. After 13 weeks a significant improvement was obtained in the hyaluronic acid group. In a multicenter double-blind study Wobig et al. (19) compared a saline solution with sodium hyaluronate. Three IA injections were administered once a week. The hyaluronic acid group had considerably less pain on weightbearing than the saline group until 24 weeks after the last injection. Consequently, limited evidence exists that, compared to placebo, IA hyaluronic acid reduces the pain for periods from 1 month to 6 months. Except for some brief local discomfort postinjection, no major side effects have been reported. In a randomized clinical study (20) methylprednisolone was compared with hyaluronic acid. One injection was administered at weekly intervals to 90 patients for five weeks. After 60 days hyaluronic acid was found to be significantly superior to cortisone in relieving pain. Caborn et al. (21) conducted a randomized, multicenter, single-blind study, running over a period of 26 weeks and comparing Hylan G-F 20 with triamcinolone hexacetonide in 215 patients with knee osteoarthritis. The WOMAC, VAS and overall assessment scales were used to evaluate the outcome. Viscosupplementation resulted in a longer period of benefit than triamcinolone.

A meta-analysis on hyaluronic acid again showed a small beneficial effect (22). Moreover, about 80% of the benefit appeared to be due to the placebo effect of an IA injection. The positive effect was even more overestimated because studies reporting positive results are more likely to be published than negative or nonsignificant results. Further trials are recommended to search for a subgroup that responds best to IA hyaluronic acid injections. Moderate evidence also exists that aspiration in itself is as effective as injections. In a single-center, prospective, open study (23) two to three IA hyaluronic acid injections were administered at weekly intervals to 20 patients with severe pain due to rhizarthrosis. The outcome assessment parameters were the VAS scale, grip strength, joint motion, crepitation during passive movement, and the global clinical impression of patients and investigator. It appeared that hyaluronic acid could be recommended for the treatment of rhizarthrosis because of its favourable effect on the above-mentioned parameters and the absence of adverse effects. In a very recent study of Petrella et al. (24), 537 patients with knee osteoarthritis received 3 IA hyaluronic acid (500-730 kD) injections at weekly intervals. A second identical course was given if the patient so desired. The interval between the first and second course was 27±7 weeks. The duration of follow-up was 6 months. The outcome was assessed by means of the VAS scale at rest and on walking, and a 5-point global satisfaction score. This prospective study covered a period of 6.7 years. Both after the first and second course of injections a significant improvement was noted in the VAS and global satisfaction scores. The patients reported very few adverse effects and required less concomitant therapies. This study showed some effect of IA hyaluronic acid in the long term.

More and more data support a predominantly symptomatic

effect of IA hyaluronic acid, but a placebo effect cannot be ruled out. High-molecular weight products would be more effective (25). A chondroprotective effect has not been clearly demonstrated. Compared to standard corticosteroid injections, the cost is about 8 times higher and the efficacy is equal (26). Moderate evidence has been provided that IA hyaluronic acid actually works. Its long-term efficacy needs to be assessed, usually over a period of six months.

A multicentre, randomized, placebo-controlled, double-blind study in 335 patients with knee osteoarthritis was presented by Joergensen during the Eular 2005 Congress (27). Intra-articulair injections of 2 ml Hyalgan and 2 ml saline solution (placebo) were administered once a week for 5 weeks. The outcome was measured by the Lequesne algo-functional index, patients global assessment, pain during 5 m walk (100 mm VAS), Nottingham Health Profile Questionnaire, effusion and acetaminophen consumption. In patients with knee osteoarthritis five intra-articular injections of Hyalgan did not improve pain function or other outcome parameters 3, 6, 9 and 12 months after the treatment. Further examination is needed to look for subgroups that could really benefit from intra-articular hyaluronic acid.

Besides the beneficial action on symptoms and function, hyaluronic acid may also have an effect on muscle strength. A 5-week treatment with weekly hyaluronic acid injections resulted in a significant improvement of concentric and eccentric quadriceps muscle strength in patients with moderate knee osteoarthritis, suggesting a possible positive effect on the proprioceptive decline that may be present in osteoarthritis and give rise to muscle atrophy (28).

Painful knee osteoarthritis, not responding to pharmacological or non-pharmacological treatments, with moderate radiographic changes, is the best clinical indication for IA hyaluronic acid injections. Other indications include more severe knee osteoarthritic changes in patients who refuse knee replacement. IA hyaluronic acid can also be used when anti-inflammatory drugs are contraindicated or not tolerated (29).

Further studies are mandatory to establish the optimal dose, concentration and molecular weight of the product. More attention should also be paid to the economic advantages, because the favourable long-term effects reduce the need for anti-inflammatory drugs.

Only minor side effects have been encountered (30). Mild pain or swelling at the injection site may occur in 20% of patients. Watterson and Esdaile (31) reported only a 3% incidence rate of local adverse reactions per injection, which resolved within 1 to 2 days. Chen et al. (32) described six patients with granulomatous inflammation of the synovium following hyaluronic acid viscosupplementation of the knee. However, the responsible causative agent was not clearly demonstrated.

Conclusion

In the presence of acute hydrops in an osteoarthritic knee an IA corticosteroid injection following aspiration of the joint can be considered. A maximum of 3 injections can be administered at intervals of 8 to 10 days, to be repeated every 6 months if absolutely necessary. A patient with a dry and painful osteoarthritic knee can be a candidate for IA hyaluronic acid injections at weekly intervals, every 6 months if need be (33).

As for frozen shoulder, little evidence has been provided that IA corticosteroid injections would have a beneficial effect on pain and movement. The value of range-of-motion exercises has not yet been proven either. Spontaneous improvement in pain and limitation of movement might also occur.

Compared to placebo, IA corticosteroids and hyaluronic acid have no serious disadvantages, but not many advantages either.

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