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Role of Intra-Articular Steroid in Knee OA

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Abstract

Osteoarthritis (OA) is a complex "complete joint" disease followed by inflammatory cells, rather than a pure process of "wear and tear". Along with cartilage degradation, subchondral bone remodelling, synovitis degeneration of menisci and ligaments, and joint capsule hypertrophy take parts in the pathological process. Hallmark symptom of OA is pain, but correlation between pain and extent of disease is still not explainable. For the knee OA, intraarticular (IA) steroid injection is preferred as the last non-operative treatment modality, if the other non-operative treatment modalities are ineffective. IA corticosteroid injections provide short term relief in OA pain and can be used as supplement to core treatment for the relief of moderate to severe pain in OA Knee patients. The current literature and our experience suggest that IA injections are safe and have positive effects for patient contentment. But, no literature suggest that any of the IA injections agents will cause osteophytes to regress or meniscus and cartilage to regenerate in knees with substantial and irreversible cartilage and bone damage.

Keywords: knee arthritis, steroid, intraarticular, inflammation

Introduction

Osteoarthritis (OA) refers to a syndrome of clinical findings of joint pain with multifactorial etio-pathogenesis that is distinguished by the gradual loss of articular cartilage, subchondral bone remodelling, osteophyte formation and inflammatory changes of the joint [1]. Pain and loss of function in OA is a major concern for disability. OA is the most common form of joint disease and among the top 10 causes of disability worldwide [2]. With increasing obesity and aging of the population, OA hold a major burden of public health problem and an important financial issue for the global economy [3]

Conservative management of a case of osteoarthritis includes a combination of pharmacological and non-pharmacological modalities which are customized to individual patient's needs. The main aim is to reduce pain, improve quality of life and function while also limiting disease progression. Conservative techniques like physiotherapy exercises, weight reduction, patient education, use of supports- crutches, braces. Pharmacological interventions in form of non-steroidal anti-inflammatory drugs, opioids, chondroitin sulphate, and glucosamine are also used. As a last resort a non-operative modality that could be used is intra-articular injections – corticosteroids, visco-supplements, blood derived product [4,5]. The major contraindication for IA injections is septic arthritis. In the presence of overlying soft tissue infection, also there is risk of iatrogenic spread to the joint [2,4,6]

Etiopathogenesis of Osteoarthritis

OA is multi-complex disease characterised by cartilage destruction, also encompasses degeneration of menisci and ligaments, capsule hypertrophy, subchondral bone remodelling- thickening, bone cyst and synovitis.

Initially there is a focal loss of cartilage which progressively expands as changes in loading occur. This includes morphological and metabolic changes in chondrocytes, along with biochemical and structural changes in the extracellular matrix, which are under the influence of multiple enzymatic and molecular feedback loops. In OA, chondrocytes start producing inflammatory mediators in response to mechanical – articular incongruity, malalignment and inflammatory stimulation. The subchondral bone also produces similar chemicals, which participate in the degradation of the deep layer of cartilage. As articular cartilage matrix proteins get fragmented, these stimulate further matrix destruction via feedback mechanisms [8].

Age also plays a significant role in OA pathogenesis. Age related changes in chondrocytes like accumulation of advanced glycation end products, cause the cartilage to become more brittle and also enhance the production of cytokines and chemokines [14].

OA also shows features of synovial inflammation. It has been hypothesized that synovitis is a result of foreign body reaction of synovial cells to degraded intra-articular cartilage products or as a primary trigger of OA process [7,8,15-16] Synovitis further leads to activation of chondrocytes and production of inflammatory mediators which increase cartilage breakdown, thus playing a role in symptom severity and rate of cartilage degradation [9,16-18]

Inflammatory mediators play a central role in the initiation and continuation of the OA process. These mediators arise from both systemic sources like adipose tissue-adipokines, which reach the joint via subchondral bone vasculature and local inflammatory cells [7,19].

Obesity as a risk factor for OA, acts via both

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mechanical loading and also through the release of adipokines, especially from centripetal adipose tissue. These contribute to a persistent low grade inflammatory state in obese patients [10,19,20]

Currently, it has become evident that the inflammatory mediators contribute significantly to the development and progression of structural changes in the OA joint. Due to the complexity and overlapping nature of the various signalling pathways and inflammatory mediators, there is lack of consensus regarding the role of these mediators as primary or secondary regulators of cartilage pathogenesis [10]. But these can be still considered as favourable targets for future OA therapy [11]

Clinical symptoms – PAIN:

The hallmark symptom of OA is knee pain. Early OA usually presents as pain after activity, but as the disease progresses, the pain attains a more chronic and constant character [3]. Development of chronic pain has shown correlation with genetic predisposition [21]. Weight also acts as a significant contributor to pain [22]

Pain arises from richly innervated structures like the subchondral bone, periarticular muscle and ligaments, synovium, joint capsule. The articular cartilage, in adults, being avascular and aneural does not contribute to pain generation, at least in early OA. With disease progression the neurovascular invasion into the cartilage may lead to pain generation.

Walsh et al, have observed presence of sensory nerve fibres in the newly formed vascular channels seen in osteochondral angiogenesis, which act as potential sources of symptomatic pain.

Synovitis in OA, is also a major contributor to the knee pain. Synovitis is histologically characterized by infiltration of lymphocyte and macrophages, and villous hyperplasia; causing stimulation of nociceptors within the synovium.

Menisci, also act as a source of pain in OA, as they show increased vascularity and increase sensory nerves infiltration. Mapp et al [31] in a recent review, emphasized that during OA, synovium shows increase angiogenesis, and leads to ossification in osteophytes and the deep layers of articular cartilage. The authors concluded that angiogenesis contribute to structural damage and pain in OA, and suggested- angiogenesis as a potential target for new treatments. Zhang et al [33] demonstrated a relationship between fluctuation of pain severity with changes in bone marrow lesions and synovitis.

The extent to which structural pathology in OA contributes to the pain experience is still not well known, this is probably because of co-existence of the structural pathologies and variations in personal pain perception [34]. On the other hand and angiogenesis arises as a reasonable target for future treatment modalities in OA.

Corticosteroids Injections: Agents – the current set of intra-articular agents routinely used are methylprednisolone acetate, triamcinolone acetate, betamethasone acetate and betamethasone sodium phosphate, triamcinolone hexacetonide, and dexamethasone.

Comparative studies between the different agents have shown inconclusive results regarding any one specific drug [35-37] it looks like that given the correct indication, dosage, timing or application, most of the injections have similar potency. [38]

Mechanism of Action: Corticosteroids show a combination of anti-inflammatory and immunosuppressive actions. They act directly on nuclear steroid receptors, thus inhibiting the immune and inflammatory cascades at different levels. Thereby reducing vascular permeability and preventing the accumulation of inflammatory mediators [39,40] clinically these present as a reduction in redness and swelling over the joint. There is a corresponding increase in the relative viscosity and hyaluronic acid concentration [39,41]

Indications And Efficacy- corticosteroid intra articular injections show benefit in both acute and chronic inflammatory knees. Especially during episodes of OA flare, these injections lead to dramatic decrease in the acute episode of pain and also enhance joint mobility [42]. The correlation between chondrolysis and OA flare also supports using IA injections as a short term treatment modality.

Various randomized controlled trials in OA patients show that though IA corticosteroids are effective, their benefit over a placebo is short-lived, up to four weeks. A recent review by Hepper et al [44] demonstrated the short term efficacy of corticosteroids in knee OA; another meta-analysis by Bannuru et al [45] also had similar findings. A 2006 Cochrane review [43] also highlighted these short term effects of injections. A study also found IA corticosteroids to be superior to placebo on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total subscale scores at four weeks [46]. On the other hand, some studies suggest a possible benefit of up to 26 wk [47,48]. However, in the 2006 Cochrane Review, it was also stated that there was a lack of evidence for efficacy in functional improvement (e.g., stiffness, walking distance, quality of life) at any time point with IA CS injections [43].

In 1995, Gaffney et al [49] reported that joint effusion and successful aspiration of synovial fluid simultaneously with the CS injection showed better pain reduction at one week follow up. A more recent study, by Arden et al, concluded the presence of effusion and milder radiographic severity of knee OA are predictors of a good response to treatment with CS injections up to 26 wk.

However, a recent systematic review about clinical predictors of response to IA CS injection in knee OA, demonstrated no

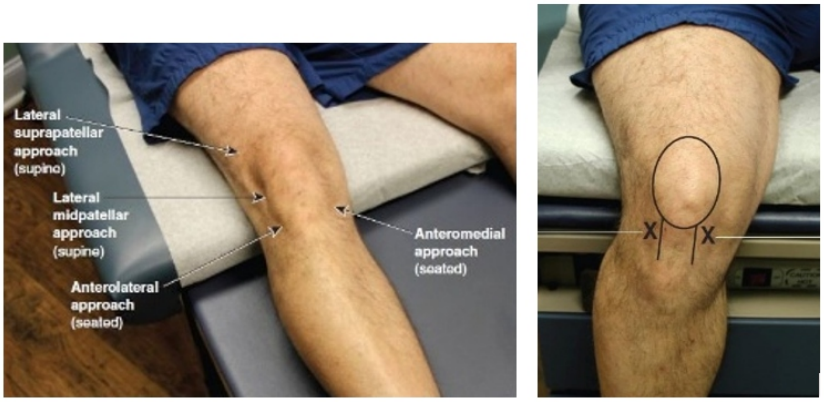

Fig1A - Sites of IA injections around the knee. 1B -Standard Antero-medial & Antero-lateral portal.

consistent predictors of response. The authors concluded that predictor factors were poorly studied in previous trials, which may be partly the cause of this result.50

Sites Of Injection - IA injections of CS in the knee joint can be given in the knee joint from multiple sites. The most commonly preferred sites are the antero-medial portal, the antero-lateral portal and supero-lateral portals.

Preperation - The usual IA injection of CS is composed of 2ml or 1 ml of Steroid formulation combined with 2% lignocaine without adrenaline or preservative. These preservatives can lead to hypersensitivity reaction in the knee joint and subsequent synovitis.

Side Effects – Usually side effects post IA CS injections are rare. Reactive flares after IA administration begin 6-12 hours after injection and resolve spontaneously in next few days [51] early studies in rodents reported the possibility of cartilage destruction [52-54]. However, subsequent studies showed that even multiple IA injections of steroids showed no significant evidence of knee cartilage degradation [55-57].

The American College of Rheumatology subcommittee on OA recommends CS injections as an effective method of decreasing pain [58]. However, American Society of Orthopaedic Surgeons work group interpreted the evidence to be inconclusive as to the benefit of IA corticosteroids and were unable to recommend for or against the use of IA corticosteroids in their guideline for patients with symptomatic OA of the knee.4

To sum up, the research evidence demonstrates that IA CS injections provide short term reduction in OA pain and can be considered as an adjunct to core treatment for the relief of moderate to severe pain in people with OA Knee [2].

Conclusions

Our experience and review of recent literature show improved patient outcomes post IA injections. But there is lack of consensus regarding whether the benefit is due to a disease modifying effect or placebo effect. The complexity and heterogeneity of OA pathology makes it hard to categorize patients or quantify level of disease for injection choice. A practical approach using patient signs and symptoms can be utilised for choosing injection. Though not every patient of OA is an ideal candidate for IA injection, it provides a promising option in non-operative management of patients with acute and persistent synovitis. A combination of medical treatment, physical medicine and rehabilitation, intra-articular injections, acupuncture, and self-management education programs should be utilised for improved clinical and functional outcomes in OA patients before going with surgical treatment.

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