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Original article

Effect of chondroitin sulphate on synovitis of knee osteoarthritic patients☆

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ABSTRACT

Objective: To evaluate by ultrasonography the effect of chondroitin sulfate (CS) on synovitis in patients with knee osteoarthritis (KOA). To collaborate in the understanding of the biochemical mechanisms involved in the synovial inflammation process.
Methods: Randomized, single-blind, controlled trial involving 70 patients with primary KOA treated for 6 months with CS or acetaminophen (ACT). Evaluation of KOA status at baseline, 6 weeks, 3 and 6 months included: ultrasonography to assess synovitis (following the OMERACT expertise group definition), visual analogue scale and Lequesne index to measure pain and function, and ELISA to quantify inflammatory mediators in serum and synovial fluid.
Results: Synovitis presence was reduced by 50% in the CS group while a 123% increase was observed in ACT group. Conversely, patients without initial synovitis and treated with ACT reached 85.71% synovitis onset, but only 25% in CS group. Both therapies improved articular function, but only CS resulted in significant pain improvement at the end of the treatment. Changes in RANTES and UCN synovial fluid concentration were associated with CS treatment.
Conclusions: Treatment with CS had a sustained beneficial effect, preventing synovitis onset or reducing its presence as well as reducing KOA symptoms. ACT ameliorated clinical symptoms but had no effect on inflammation. The CS anti-inflammatory effect could be related to the observed changes in RANTES and UCN concentration.

Efecto del condroitín sulfato en la sinovitis de pacientes con artrosis de rodilla

Palabras clave:
Artrosis de rodilla
Condroitín sulfato
Dolor
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RESUMEN

Objetivo: Evaluar mediante ecografía el efecto del condroitín sulfato (CS) en la sinovitis de pacientes con artrosis (OA) de rodilla, y colaborar en el conocimiento de los mecanismos bioquímicos involucrados en la inflamación sinovial.
Métodos: Estudio controlado, aleatorizado, ciego simple de 70 pacientes con OA de rodilla tratados durante 6 meses con CS o paracetamol (PCT). Los pacientes fueron visitados a tiempo basal, a las 6 semanas, y a los 3 y 6 meses para valorar el estado de su OA según los siguientes parámetros: sinovitis evaluada mediante ecografía (según definición de expertos OMERACT); dolor y función, mediante la escala visual analógica y el índice de Lequesne; y concentración de mediadores inflamatorios en suero y líquido sinovial, mediante ELISA.

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Resultados: El tratamiento con CS redujo en un 50% el número de individuos que presentaban sinovitis; sin embargo, se observó un incremento de un 123% en el grupo tratado con PCT. En los pacientes sin sinovitis inicial, se observó el establecimiento de esta en un 85,71 y 25% de los casos tratados con PCT y CS, respectivamente. Ambas terapias mejoraron la función articular, pero únicamente el tratamiento con CS produjo una mejora significativa del dolor al final del tratamiento. Se observó una asociación entre el tratamiento con CS y los cambios en la concentración de RANTES y UCN en el líquido sinovial.
Conclusiones: El tratamiento con CS tiene un efecto mantenido beneficioso, previniendo la aparición de sinovitis o disminuyendo su presencia, así como reduciendo los síntomas de la artrosis. El PCT también mejora los síntomas clínicos, pero no tiene ningún efecto sobre la inflamación. Las variaciones observadas en la concentración de RANTES y UCN podrían estar relacionadas con el efecto antiinflamatorio asociado al tratamiento con CS.

Introduction

Osteoarthritis (OA) is the most prevalent musculoskeletal disease. It affects about 3.6% of the population worldwide, is a leading cause of chronic disability, and is associated with elevated healthcare and socioeconomic costs.[1] At the histological level, it is characterized by progressive articular degeneration with an underlying chronic inflammation, accompanied by osteophytes, degradation of cartilage, changes in subchondral bone, and varying degrees of synovial inflammation (synovitis). Although synovitis was initially considered a late phenomenon in the disease course, it is now recognized and documented as an early hallmark linked to development of pain and progression of structural damage.[2] Therefore, its detection could be clinically useful not only for understanding the individual patient's OA progression, but also for the development of new treatments that may achieve better outcomes. In 2005 an OMERACT group of experts published both the definition of synovitis and the guidelines for its ultrasound identification. Their definition of synovitis as the presence of synovial hypertrophy and/or joint effusion provides high sensitivity and specificity in both clinical and research settings.[3,4]

The onset and persistence of synovitis is influenced by multiple pathways and inflammatory mediators, including pro-inflammatory cytokines, nitric oxide (NO), prostaglandin E_2 (PGE_2), chemokines, substance P, and several neuropeptides. Among pro-inflammatory cytokines, IL-1β has a central role in the physiopathology of OA through the induction of matrix metalloproteinases (MMPs), the stimulation of NO production (as well as other pro-inflammatory cytokines), and the induction of chondrocyte apoptosis.[5,6] On the other hand, chemokines are potent mediators of the cell adhesion and migration involved in leucocyte trafficking and angiogenesis regulation. Various chemokines have been detected in the synovial fluid (SF) of OA patients, such as IL-8 (CXCL-8), chemokine (C-X-C motif) ligand 16 (CXCL-16), fractalkine (CX_3CL1), monocyte chemoattractant protein-1 (MCP-1/CCL2), and Regulated on Activation, Normal T-cell Expressed and Secreted (RANTES/CCL5), among others.[7–11] Finally, some neuropeptides, such as corticotropin-releasing factor (CRF), urocortin (UCN), and vasoactive intestinal peptide (VIP), modulate the expression of inflammatory and extracellular matrix remodelling mediators, contributing to OA pathogenesis.[12] At a local level, CRF and UCN are secreted to the OA joint environment and regulate inflammation.[13,14] The presence and interrelationships of these NPs and their receptors has been described in fibroblast-like synoviocytes (FLS) from OA patients.[15,16]

Current OA management includes non-pharmacological, pharmacological, and surgical treatments. Pharmacological therapies are mainly medications that reduce symptoms, such as anti-inflammatory and analgesic agents, and symptomatic slow-acting drugs for osteoarthritis (SYSADOAs), which also may exert beneficial structural changes on OA joints.[17] These agents include glucosamine, chondroitin sulfate (CS), and hyaluronic acid, among others.

Several in vitro and in vivo studies have suggested that CS, a natural glycosaminoglycan and a major component of the extracellular matrix of the cartilage, has anti-inflammatory, anabolic, anti-catabolic, and anti-apoptotic properties.[18] Anti-inflammatory effects are exerted through inhibition of NO synthase, reduction in cytokine release, and decreased PGE_2 levels.[19] Anti-catabolic and anabolic properties are linked to CS capacity to induce synthesis of proteoglycans and various collagen types and to inhibit some collagenases and aggrecanases.[20] Furthermore, the anti-apoptotic effects of CS are associated with reduced translocation of nuclear factor κB (NF-κB), impairment of the MAP kinase-signalling pathway, and the inhibition of caspase-3 and -7 activation.[19]

At the clinical level, although the evidence describing the utility of CS in the treatment of OA patients shows some controversy,[21] there are several clinical trials[22,23] and meta-analyses[24,25] that describes CS as a useful treatment to improve symptoms and modify joint structure. Data from the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) showed that CS treatment did significantly improved clinical manifestation of synovitis such as knee joint swelling and/or effusion at 6 months follow-up.[26] In this study, synovial inflammation was evaluated by clinical examination. There have been recent advances in the assessment of synovitis by means of imaging techniques as musculoskeletal ultrasound, which is much more sensitive.

The primary aim of the present pilot study was to evaluate the effect of CS on synovitis in knee osteoarthritis (KOA) by ultrasound, following the definitions of the OMERACT expertise group.[4] KOA patients treated with acetaminophen (ACT) were used as control group. In addition, in an effort to contribute to understanding the biochemical mechanisms involved in the synovial inflammation process, plasma and SF levels of several pro-inflammatory cytokines, chemokines, and neuropeptides were determined and correlated with synovitis presence. Finally, these outcomes were compared between the two treatment groups.

Methods

Study design and participants

This randomized, single-blind, controlled trial was carried out at the Rheumatology Unit of Hospital del Mar in Barcelona, Spain. Seventy KOA patients aged ≥40 years were enrolled in the study.

Main inclusion criteria were fulfilment of the American College of Rheumatology (ACR) classification criteria for clinical KOA[27]; the presence of radiographic OA in the knee joint, defined as a Kellgren and Lawrence (K&L) score of 2 or 3; and the presence of joint swelling or effusion upon clinical examination. Main exclusion criteria included any serious disease (such as decompensated heart disease, diabetes, fibromyalgia, kidney failure, liver