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Original article

Effects of chondroitin sulfate on brain response to painful stimulation in knee osteoarthritis patients. A randomized, double-blind, placebo-controlled functional magnetic resonance imaging study☆

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ABSTRACT

Introduction: Knee osteoarthritis is causing pain and functional disability. One of the inherent problems with efficacy assessment of pain medication was the lack of objective pain measurements, but functional magnetic resonance imaging (fMRI) has emerged as a useful means to objectify brain response to painful stimulation. We have investigated the effect of chondroitin sulfate (CS) on brain response to knee painful stimulation in patients with knee osteoarthritis using fMRI.
Methods: Twenty-two patients received CS (800 mg/day) and 27 patients placebo, and were assessed at baseline and after 4 months of treatment. Two fMRI tests were conducted in each session by applying painful pressure on the knee interline and on the patella surface. The outcome measurement was attenuation of the response evoked by knee painful stimulation in the brain.
Results: fMRI of patella pain showed significantly greater activation reduction under CS compared with placebo in the region of the mesencephalic periaquecductal gray. The CS group, additionally showed pre/post-treatment activation reduction in the cortical representation of the leg. No effects of CS were detected using the interline pressure test.
Conclusions: fMRI was sensitive to objectify CS effects on brain response to painful pressure on patellofemoral cartilage, which is consistent with the known CS action on chondrocyte regeneration. The current work yields further support to the utility of fMRI to objectify treatment effects on osteoarthritis pain.

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Efectos del condroitín sulfato sobre la respuesta cerebral a la estimulación dolorosa en pacientes con artrosis de rodilla. Estudio de resonancia magnética funcional aleatorizado, doble ciego y controlado con placebo

Palabras clave:
Resonancia magnética funcional
Artrosis de rodilla
Dolor
Condroitín sulfato

R E S U M E N

Introducción: La artrosis de rodilla es causa de dolor e incapacidad funcional. Uno de los problemas para evaluar la eficacia de los analgésicos ha sido la falta de medidas objetivas de dolor, aunque la resonancia magnética funcional (RMf) ha surgido como un medio útil para objetivar la respuesta del cerebro a la estimulación dolorosa. Hemos investigado el efecto del condroitín sulfato (CS) sobre la respuesta del cerebro a la estimulación dolorosa de la rodilla en pacientes con artrosis mediante RMf.
Métodos: Veintidós pacientes recibieron CS (800 mg/día) y 27 placebo y fueron evaluados inicialmente y después de 4 meses de tratamiento. En cada sesión de RMf se aplicó presión dolorosa sobre la interlínea de la rodilla y en la superficie de la rótula. El resultado se cuantificó como la atenuación de la respuesta cerebral a la estimulación dolorosa de la rodilla.
Resultados: La RMf de la maniobra rotuliana mostró una reducción de la activación en la región de la sustancia gris periacueductal del mesencéfalo significativamente mayor durante el tratamiento con CS que en la condición de placebo. El grupo de CS, pero no el de placebo, mostró además una reducción de la activación en la representación cortical de la pierna tras el tratamiento. No se observaron efectos del CS con presión dolorosa sobre la interlínea de la rodilla.
Conclusiones: La RMf fue sensible para objetivar los efectos del CS sobre la respuesta del cerebro a la presión dolorosa sobre el cartílago rotuliano-femoral, que es un resultado coherente con la acción conocida del CS sobre la regeneración de los condrocitos. El presente trabajo muestra nuevamente la utilidad de la RMf para objetivar los efectos del tratamiento en el dolor de origen artrósico.

Introduction

The knee is a key element for pedestrian humans to stand and walk. It is the most robust joint in the body supporting nearly the whole weight during erect activity. Nevertheless, the burden of work throughout life favors knee osteoarthritic degeneration, which is a frequent cause of chronic pain and functional disability.[1]

A variety of treatments have been tested to alleviate knee osteoarthritis symptoms, most being focused on reducing pain through analgesic or anti-inflammatory actions. Of particular interest, however, are agents aiming at improving patients' clinical situation by interfering with the progression of structural changes in joint tissues. Clinical studies have reported a beneficial effect of pharmaceutical-grade chondroitin sulfate (CS) on knee pain, and a parallel small but significant reduction in the rate of decline in joint space width.[2–6] Nevertheless, not all clinical trials have been successful.[7]

Inherent problems with efficacy assessment of pain medication are the lack of objective pain measurements and the large variability of subjective pain ratings.[8]

Noninvasive neuroimaging has emerged as a useful means to objectify brain response to painful stimulation. In particular, functional magnetic resonance imaging (fMRI) has proved its ability to comprehensively map brain activity associated with pain experience.[9] Although there are only few imaging studies on knee osteoarthritis,[10–13] previous work has already characterized brain activity associated with evoked pain, spontaneous pain[10,14] and pain modulation[11] in knee osteoarthritis patients. Two studies have specifically tested analgesic treatment in knee osteoarthritis using lidocaine patches[13] and single-dose naproxen.[12] Interestingly, in both studies, the treatment effect on brain activity attenuation was more evident than on subjective pain score reduction, suggesting the potential usefulness of fMRI to complement the testing of drug effects on pain.

Within the anatomically complex knee, the medial tibiofemoral articular interline is one of the most tender points.[15] Pressure on this site in patients with knee osteoarthritis may generate pain from damage or sensitization in a variety of structures (e.g., lateral ligament, joint capsule, synovium, outer edge of the internal meniscus and subchondral bone).[16] Thus, stimulating this point using focal pressure is a highly sensitive maneuver to elicit pain.[15] On the other hand, the pain generated by pressing down the patella surface in osteoarthritic knees is probably less complex, and may be more selectively related to sensitization processes in the bone and the junction between the bone and cartilage as a result of erosion in the patella and femoral cartilages.[16,17] Agents like CS potentially may improve pain generated in both knee sites, but patella manipulation could be more suitable to identify treatment actions on the cartilage.

The aim of the present fMRI study was to objectively identify the effects of four-month CS treatment on the brain response to pressure painful stimulation in patients with symptomatic knee osteoarthritis. We hypothesized that attenuation of the response evoked in the pain-processing brain system under knee pressure would be a sensitive outcome measurement to capture CS effects on knee osteoarthritic pain.

Methods

Study population

The current study was developed in the Rheumatology Department and the MRI Research Unit of the Hospital del Mar in Barcelona, from December 2010 to January 2013. Patients attended the Hospital del Mar's services or referred to it from primary health care centers. A total of 78 patients with radiological grade II or III[18] and clinical osteoarthritis based on the American College of Rheumatology (ACR) criteria[19] were screened from whom 64 were randomized (32 to placebo and 32 to CS) (see Suppl. file for eligibility and exclusion criteria and for sample size assumptions). Thirteen patients dropped-out of the study and two more were excluded from the analysis. Finally, 49 patients were evaluable, including 27 in the placebo group and 22 in the CS group (see Fig. 1 for patient flow diagram and Table 1 for patient characteristics).[20,21]

Written informed consent was obtained from all the patients. The study was approved by the local Ethics Committee (Clinical