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The effects of nonsteroidal anti-inflammatory drugs on clinical outcomes, synovial fluid cytokine concentration and signal transduction pathways in knee osteoarthritis. A randomized open label trial

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SUMMARY

Objective: We investigated the effects of celecoxib, diclofenac, and ibuprofen on the disease-specific quality of life, synovial fluid cytokines and signal transduction pathways in symptomatic knee osteoarthritis (OA).

Design: Ninety patients scheduled for a total knee arthroplasty (TKA) were randomized to six groups that were treated with low and high dosages of celecoxib, diclofenac or ibuprofen. At the time of the first admission (T0) and at surgery (T1 = 14 days after beginning of the nonsteroidal anti-inflammatory drugs (NSAIDs)), samples of knee synovial fluid were obtained from each patient for analysis. During the surgery the synovial tissue was harvested from the knee of patients. The Western Ontario and McMaster universities (WOMAC) score was used to evaluate the patient disease-specific quality of life at T0 and T1. Microarray tests performed at T0 and T1 were used to evaluate the effects of NSAIDs on Tumor necrosis factor (TNF)-alpha, Interleukin-6 (IL-6), IL8 and Vascular endothelial growth factor (VEGF) concentration in the synovial fluid. Western blot assays evaluated the effects of NSAIDs on MAP kinase (MAPK) signal transduction pathway in the synovial membrane.

Results: NSAID treatment induced a statistically significant improvement in the WOMAC score and a statistically significant decrease in the IL-6, VEGF and TNF-alpha concentration in the synovial fluid. Higher dosages of NSAIDs provided a greater improvement in the disease-specific quality of life of patients and lower concentrations of pro-inflammatory cytokines in the synovial fluid. Inhibition of MAPKs was noted after NSAID treatment.

Conclusion: Short-term NSAID treatment improves the patient disease-specific quality of life with a parallel decrease in pro-inflammatory synovial fluid cytokine levels in knee OA. Signal transduction pathways may be involved in regulating the anti-inflammatory effects of NSAIDs.

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Introduction

Central mechanisms may play a role in pain perception during osteoarthritis (OA). However, local inflammation (which involves production of pro-inflammatory cytokines such as interleukin (IL) Tumor necrosis factor (TNF)-alpha, Interleukin-6 (IL-6) and IL-8) is considered to be a major source of pain. In addition to their role in the pathomechanisms of osteoarthritic pain, synovial fluid cytokines

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may in turn contribute to joint destruction and exacerbation of nociception[1]. Several cytokines have been detected in the synovial fluid of patients with early OA[2]. Among these, TNF-alpha and IL-6 were found in 96.1% and 84.6% of OA synovial fluid samples, respectively[3]. TNF-alpha is the major pro-inflammatory cytokine responsible for the shift of cartilage homeostasis towards more catabolism and degradation of the cartilage[4]. In details, it activates sensory neurons directly via its receptors[5], increases the synthesis of other pro-inflammatory cytokines such as IL-6 and IL-8[6] and contributes to loss of the cartilage matrix[7]. Indeed, it induces the synthesis of Matrix metalloproteinases (MMPs) and other proteinases by chondrocytes and suppresses cartilage anabolism by inhibiting the synthesis of proteoglycans and type II collagen[8]. IL-6 levels in the synovial fluid are related to the OA stage[9], and they contribute to cartilage degradation in OA[10]. Moreover, IL-6 could facilitate the excitatory action of substance P on dorsal root ganglion neurons[11]. Vascular endothelial growth factor (VEGF) and its receptors are expressed in OA cartilage and the synovial pannus and are involved in the angiogenesis associated with cartilage destruction during OA[12]. MAP kinase (MAPK) pathways play a significant role in inflammation and OA. It has been demonstrated that MAPK pathways are able to modulate cytokine-induced chondrocyte responses[13].

Certain therapies that specifically interfere with the expression or actions of pro-inflammatory cytokines have been explored[14,15]. nonsteroidal anti-inflammatory drugs (NSAIDs) have analgesic, antipyretic and anti-inflammatory properties and are extensively prescribed for several musculoskeletal disorders. Indeed, the Osteoarthritis Research Society International (OARSI) recently recommended the use of NSAIDs for management of knee and hip OA in symptomatic patients[16]. These drugs have been shown to influence cytokine metabolism in the synovial fluid of OA patients with satisfactory relief of painful osteoarthritic joints[17–19].

The aim of the current study was to explore whether selected NSAID treatment inhibits TNF-alpha, IL-6, IL-8, and VEGF secretion in the synovial fluid of osteoarthritic joints. Diclofenac, ibuprofen and celecoxib were studied. Under the hypothesis that relationships between pro-inflammatory cytokines and the clinical status of OA patients are possible, we also evaluated the association between the concentration of these molecules in the osteoarthritic knee synovial fluid and the pain and functional status of patients with OA. The effects of selected NSAIDs on signal transduction pathways in the synovial membrane were also investigated.

Materials and methods

Study population

From April 2010 to August 2011, 128 patients were evaluated at the Department of Orthopaedic and Trauma Surgery of the Magna Græcia University (Catanzaro, Italy) for primary knee OA and scheduled for a total knee arthroplasty (TKA). Patients eligible for this randomized, open label, parallel-group, single center study should be older than 50 years and should have primary knee OA diagnosed according to the clinical and radiological criteria of the American Rheumatism Association[20]. Further inclusion criteria were clinical signs of joint inflammation (warmth, swelling or effusion) and a disease severity grade 2 or 3 according to the Kellgren–Lawrence (KL) classification[21].

Patients who met the following conditions were excluded: allergy to NSAIDs, progressive serious medical conditions (such as cancer, AIDS or end-stage renal disease), history of gastrointestinal ulcer or bleeding, a hemoglobin concentration lower than 11.5 g/dL, renal diseases (serum creatinine concentration more than 1.2 times the upper limit of the normal range according to the central laboratory definition reference values), or liver dysfunction (serum alanine or aspartate transaminase concentrations more than 1.5 times the upper limit of normal range according to the central laboratory definition reference values). Other exclusion criteria were a diagnosis of rheumatoid arthritis based on the physical examination and laboratory data, alcohol consumption (consuming >3 alcoholic beverages daily) and substance abuse, anticoagulant treatment and inability to give informed consent. Patients were also excluded if they were currently, or within the 3 months prior to inclusion, being treated with corticosteroids or indomethacin. Patients who received intra-articular treatment with corticosteroids or hyaluronic acid within 6 months preceding the study or systemic NSAIDs within 15 days before the study were also excluded. Finally, patients with other painful conditions, or on medication that could possibly confound the evaluation of pain relief (i.e., opioids, paracetamole, corticosteroids, antiepileptics, benzodiazepines and antidepressants), were also excluded.

This study was approved by the Researchers Ethics Committee (number 2010.29) and was conducted in accordance with the Declaration of Helsinki and the Guideline for Good Clinical Practice. All of the participants signed written informed consent prior to enrollment.

Experimental protocol

In this study the eligible patients were randomized into six study groups for treatment (all of the groups consisted of 15 patients), and for 2 weeks an oral dose of the following NSAIDs were given: diclofenac slow release 75 mg/once day or 75 mg/bid (Novartis Pharmaceuticals UK Ltd, Camberley, UK); ibuprofen 600 mg/bid or 600 mg/tid (Abbott laboratories SPA, Campoverde Latina, Italy); or celecoxib 200 mg/once day or 200 mg/bid (Pfizer Inc, New York, NY, USA) (Fig. 1). The patients were allocated using a randomized list produced by a computer-generated table in order to ensure that there were no relevant differences among the study groups with respect to age, sex, OA stage and The Western Ontario and McMaster universities (WOMAC) score.

Clinical assessment

WOMAC osteoarthritis index score was used to measure the disease-specific health status of patients before and after the pharmacological treatment[22]. The WOMAC is a self-administered validated outcome measure that evaluates pain (five items), stiffness (two items), and physical function (17 items). A total WOMAC summary score is calculated for each individual, adjusted, and reported on a 0–100 scale. Lower scores are associated with less pain and stiffness and better function. The safety of the study medications was assessed by monitoring for any adverse drug reactions (ADRs), which were assessed for severity and causality. The severity of ADRs was assessed by a modified Hartwig and Siegel scale that classifies the severity of an ADR as mild, moderate or severe with various levels according to factors such as requirement for change in treatment, duration of hospital stay, and any disability produced by the ADR[23]. To evaluate the relationship between ADRs and drug treatment, the Naranjo adverse probability scale was applied[24]. The Naranjo scale consists of objective questions with three types of responses (yes, no or do not know). The scores are given accordingly and the drug reactions are classified as definite, probable or possible.

The number, duration, and severity of pain attacks, analgesic intake and the occurrence of adverse events were recorded in a daily diary card 1 week prior to the start of the trial and up to 7 days after the surgery. The total blood loss related to TKA was evaluated as previously described[25]. The overall clinical response during the study was assessed by physicians who were blinded to the treatment.

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