SOCIEDADE BRASILEIRA DE ORTOPEDIA E TRAUMATOLOGIA

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Original Article

Intra-articular viscosupplementation of hyaluronic acids in an experimental osteoarthritis model☆

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ARTICLE INFO

Article history:
Received 8 March 2017
Accepted 6 April 2017
Available online 4 April 2018

Keywords:
Osteoarthritis
Hyaluronic acid
Experimental model of osteoarthritis
Immunohistochemistry

ABSTRACT

Objective: To analyze, from the immunohistochemical perspective, the effects of hyaluronic acid of different molecular weights in an experimental model of osteoarthritis in rabbits.
Methods: Forty-four male California rabbits were randomly assigned to three different groups (PR, S, and P) and submitted to the resection of the anterior cruciate ligament of the right knee. Three weeks after the surgical procedure, three intra-articular weekly injections were carried out with low-molecular-weight native hyaluronic acid (Hyalgan®) to PR group, high molecular weight branched chain hyaluronic acid (Synvisc®) to group S, and saline solution 0.9% to group P. All animals were sacrificed 12 weeks after the surgical procedure, and the tibial plateaus of the infiltrated knees were then dissected. Histological sections of cartilage from the tibial plateau support areas were stained with immunohistochemical markers in order to investigate the amount of metalloproteases (MMPs 3 and 13) and their inhibitors (TIMPs 1 and 3). The staining intensity was quantified on a Zeiss Imager.Z2 Metasystems microscope and analyzed by Metafer4 Msearch software.
Results: The chondroprotective effect of the hyaluronic acids used in the study was demonstrated when compared to the control group. However, the comparison between them presented no significant statistical difference regarding chondroprotection.
Conclusion: The injection of saline solution demonstrated signs of OA development, while adding native hyaluronic acid of low molecular weight (Hyalgan®) and hyaluronic acid of high molecular weight (Synvisc®) protected the articular cartilage in this model of OA.

☆ Study conducted at the Universidade Federal do Paraná (UFPR), Departamento de Ortopedia e Traumatologia, Curitiba, PR, Brazil.

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https://doi.org/10.1016/j.rboe.2018.03.009

Viscossuplementação intra-articular de ácidos hialurônicos em modelo experimental de osteoartrite

Palavras-chave:
Osteoartrite
Ácido hialurônico
Modelo experimental de osteoartrite
Imuno-histoquímica

RESUMO

Objetivo: Analisar do ponto de vista imuno-histoquímico os efeitos do ácido hialurônico de diferentes pesos moleculares em modelo experimental em coelhos.
Métodos: Foram alocados de modo aleatório 44 coelhos da raça California, machos, em três grupos (PR, S e P), e submetidos à ressecção do ligamento cruzado anterior do joelho direito. Decorridas três semanas do procedimento cirúrgico iniciaram-se as três injeções intra-articulares semanais de ácido hialurônico nativo de baixo peso molecular (Polireumin®) no grupo PR, ácido hialurônico de cadeia ramificada de alto peso molecular (Synvisc®) no grupo S e soro fisiológico 0,9% no grupo P. Todos os animais foram sacrificados após 12 semanas do ato cirúrgico e os platôs tibiais dos joelhos infiltrados foram dissecados. Cortes histológicos da cartilagem das áreas de apoio dos platôs tibiais foram corados com marcadores imuno-histoquímicos para pesquisa da quantidade de metaloproteases (MMPs-3,13) e seus inibidores (TIMPs-1,3). A intensidade de coloração foi quantificada em um aparelho de microscopia Zeiss Imager.Z2 Metasystems e analisada pelo *software* Metafer4 Msearch.
Resultado: O efeito condroprotetor dos ácidos hialurônicos usados no estudo foi demonstrado quando comparados com o grupo controle, porém feita a comparação entre si não houve diferença estatística significante quanto à condroproteção.
Conclusão: A injeção de solução salina demonstra sinais de desenvolvimento de OA enquanto que a adição de ácido hialurônico nativo de baixo peso molecular (Polireumin®) e ácido hialurônico de cadeia ramificada de alto peso molecular (Synvisc®) protegeram a cartilagem articular nesse modelo de OA.

Introduction

Osteoarthrosis is the most common joint affection in the knee; it is defined by specific structural alterations of the joint, including: focal degradation of the articular cartilage, inflammatory processes in the synovial tissue, biochemical changes in the synovial fluid and remodeling of the subchondral bone with osteophyte formation in the margins of the joint. It is currently defined as an inflammatory joint disease, and now it is termed osteoarthritis (OA), being no longer considered a simple joint degeneration.

The pathology is a major cause of activity limitation, physical restraint, overuse of healthcare services, and reduced quality of life, especially in people over 45 years.[1] Recent researches indicate an increase in the prevalence of this condition, as 27 millions of adults in the United States over 25 years old show clinical signs of OA in the hand, knee, or hip, an increase from the 21 million in 1995. In the population above 45 years, 19–28% present radiologically-confirmed OA; it is considered the most common chronic arthritis in the world.[2]

In Brazil, disease costs are harder to estimate due to lack of official statistics, but given that the incidence of OA is directly proportional to population aging, national costs also tend to increase. As in 2016 the Brazil had 207 million inhabitants, 22.69% of whom in the range of young individuals and 8.17% in that of elderly individuals. According to projections of the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística [IBGE]), by 2030 the country will have 223 million inhabitants, 17.59% in the youth age group and 13.44% in the elderly group, that is, a relative increase of 64% in the elderly population in the country.[3]

OA is the result of several factors in joint dysfunction; its functional failure is characterized by cartilage degeneration, joint inflammation, and simultaneous proliferation of bone, cartilage, and connective tissue.[4–6] Among the various treatment modalities currently available, intra-articular injections of hyaluronic acid (HA) have demonstrated beneficial effects in the control of knee OA symptoms (gonarthrosis).[7]

HA, administered as intra-articular injections, may potentiate the regenerative effects of endogenous HA on articular cartilage, restore the viscoelasticity of synovial fluid, contribute to the synthesis of endogenous HA and other components of the extracellular matrix by synoviocytes, and prevent the degradation of proteoglycans and extracellular matrix collagen fibers. HA also stimulates chondrocyte metabolism and prevents its apoptosis; it also inhibits chondral degradation and inflammatory joint responses.[8] These effects are attributed not only to HA's ability to reduce OA-related symptoms, but also to its interference in the progression of inflammatory processes and joint degeneration.[9,10]

In order to evaluate the effects of these substances on OA, the authors proposed the use of an already-established experimental model of OA that resembles that observed in the human species, the section of the anterior cruciate ligament (ACL) of the knee of rabbits (stifle) mimics the morphological and biochemical changes observed in human OA, which allows an accurate reproduction of the results obtained.[11,12]