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Hyaluronic acid protected from oxidation by Adelmidrol provides effective long-term pain relief in patients with adhesive capsulitis of the shoulder

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Abstract

Introduction
Adhesive capsulitis (AC) or frozen shoulder is characterized by joint stiffness and pain [1]. Overproduction of reactive oxygen species in the inflamed shoulder is responsible for damaging joint cells as well as body's own or injected biomolecules (e.g., hyaluronic acid), with negative consequences on intrinsic viscosity and lubricating properties [2]. Although AC is self-limiting, patients may experience a long-term condition of severe functional limitation and pain (up to 3 years). Current medications provide pain relief in the short-term, while long-term outcomes are still unsatisfactory. Here we investigated whether Adelmidrol, i.e., a palmitoylethanolamide analogue [3], protects hyaluronan against oxidative degradation and further described two cases of AC, managed through a multimodal approach comprising intra-articular injections of high molecular weight hyaluronic acid (1%, MW1300-2000 kDa) and Adelmidrol (2%).

Methods
Oxidative degradation of a sodium hyaluronate (1%) solution was induced by adding 70 µL $CuSO_4$ (0.1M) and 25 µL of EDTA (0.22 mM) followed by 1 mL hydrogen peroxide (30%). The effect of Adelmidrol (final 2% concentration) on hyaluronan oxidative degradation was assessed by the changes of the dynamic viscosity using a rotational viscometer. Case 1- a 57-year-old woman diagnosed primary AC with supraspinatus tendinopathy. Case 2- a 71-year-old woman diagnosed secondary AC after a proximal humerus fracture. Three fortnightly intra-articular injections of Hyadrol® (hyaluronan 1% and Adelmidrol 2%) were added, during the second or third 10-session physical therapy of one month's duration, respectively. Treatment effect was monitored by measuring (i) pain severity at the Numeric Rating Scale (NRS), (ii) upper limb function, through the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire, which allows the patient to rate activities of daily living (ADL) [4].

Results
The oxidative depolymerization of hyaluronan was greatly counteracted by Adelmidrol, as more than 50% inhibition of viscosity reduction was observed at 30 min.
Severe pain and limited range of motion were present in both patients at the first visit. Two weeks after the third and last Hyadrol® injection, shoulder pain significantly improved on NRS, from a baseline score of 9 to a score of 1 and 0, in the first and second case, respectively. Range of motion recovered to the level of uninvolved contralateral side, and ADL significantly improved on DASH score. At 6-month follow-up after the last visit, patient 1 reported complete motor relief with only minimal pain; patient 2 reported persistence of the acquired relief on movements and remained pain-free (NRS 0).

Conclusions
The study shows for the first time that Adelmidrol protects hyaluronic acid against oxidation. In accordance with previous trials [4,5], it also suggests that the duration of the effect of intra-articular hyaluronan may be prolonged in AC patients if the lubricating biopolymer is preserved against oxidative degradation by Adelmidrol.

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