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# Report Review: Pronolis HD®, the First High Density Hyaluronic Acid Gel for Intra-Articular in Osteoarthritis: Complete and Innovative Range of Viscosupplementation for all Synovial Joints

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## Abstract

Osteoarthritis (OA) is a common and debilitating condition associated with pain and loss of mobility that undermines patients' quality of life. OA is a degenerative joint disease characterized by an accumulation of mechanical stresses to the joints, leading to the destruction of articular cartilage. In OA of the knee, both synovial fluid elastoviscosity and hyaluronan concentration are reduced. For compensation, intraarticular injection of a hyaluronic acid (HA) viscoelastic gel is applied to the affected joint, also referred to as viscosupplementation (VS). Current evidence indicates that HA injections are beneficial and safe for patients with OA of the knee. Intraarticular injections of HA treat the symptoms of knee OA and may also have disease-modifying properties, potentially delaying progression of OA [1].

Hyaluronic acid is a natural component, present also in the synovial fluid of the human body. In the synovial fluid, it serves as lubricant of the joints. Meanwhile, since more than 30 years, industrial manufactured HA is used for treatment of OA [2-4].

In the past, OA was not considered an inflammatory disorder, but nowadays it is associated with several inflammatory mediators. Finding a way to modulate these inflammatory mediators could lead to new insights into the treatment of this pathologic condition [6].

This technical evaluation of PRONOLIS HD shows a safety and efficacy profile similar to the rest of single-injection Hyaluronic acids used in clinical practice. PRONOLIS HD, a newly released range of products of the Procare Health Iberia Company located in Spain, has been approved as the first high density HA gel with complete and innovative range of viscosupplementation [7].

***Keywords:*** *Pronolis HD; Hyaluronic Acid; Viscosupplementation*

## Introduction

Primary osteoarthritis (OA) of the knee is a disease characterized by the deterioration and loss of hyaline articular cartilage, alterations of the subchondral bone as well as the synovial membrane and rest of the periarticular soft tissues.

OA is the most frequent joint disease, with a risk of suffering 2.6 times higher in women than in men [1]. Its frequency increases with age, and in those over 60 years, it is estimated that more than 80% have radiological alterations of OA in at least one joint. The importance of knee OA lies in its high frequency, the discomfort it causes and the significant functional deterioration especially in the knees and hips of patients. Although Platelet-Rich Plasma injections are useful in mild to moderate degree of OA (not for advanced OA with knee deformit) [8], Hyaluronic Acid have appeared for 2 decades to be a safe and effective treatment of mild to moderate OA, an may be helpful in advanced stages of knee OA [9].

During the development of the knee OA, both the concentration of HA in the synovial fluid and its degree of polymerization decrease due to the action of superoxide ions and a decrease in synthesis by the synovitis [10]. Therefore, viscosupplementation- i.e. intra-articular injection of HA- has been also used during the last decade to improve the biomechanical functions of the synovial fluid, decreasing the release of pro-inflammatory enzymes and pain-producing neuropeptides.

## Hyaluronic Acid

### Mechanism of Action

HA has shown positive effects on cartilage anabolism. Thus, HA increases the synthesis of Prostaglandins (PG) in equine articular cartilage [11] and in rabbit chondrocytes [12]. Similarly, HA inhibits the deleterious effect of IL-1β on the synthesis of PG in human cartilage from patients with OA [13]. Also in human cartilage, HA has been shown to block the depletion of PG produced by fragments of fibronectin [14].

Several studies have highlighted the ability of HA to modulate mediators of inflammation. Takahashi., *et al*. [8] showed that HA reduces the synthesis of IL-1β in rabbit synoviocytes in which an early-onset OA was reproduced under experimental conditions. The HA attenuates the fibrinolytic activity mediated by the urokinase-type plasminogen activator (u-PA) and its receptor (u-PAR) [9]. HA reduces the production of PGE2 induced by IL-1 in a dose-dependent manner in cell cultures of synoviocytes from arthritic patients [15].

The HA has antioxidant effects that were revealed when it was found that HA itself and one of its components, D-glucuronic acid, were able to decrease reactive oxygen species (ROS) in two systems capable of generating these oxidizing molecules [16]. Fukuda., et al. obtained the same results when they evaluated ROS in bovine cartilage treated with HA [17]. The antioxidant effect of HA was also proposed by Takahashi K., *et al*. when they demonstrated, in cultures of rabbit chondrocytes, an OA had been provoked, that HA was capable of decreasing Nitric Oxide synthesis [18].

### Clinical Efficacy

Several studies have been carried out to check the therapeutic efficacy of the different types of HA for the treatment of knee OA and to a lesser extent hip, hand, shoulder, and ankle. In most of them, positive results have been obtained regarding the improvement of pain and function.

Two meta-analyses carried out by Lo., *et al.* [19] and Wang., *et al.* [20] have shown that the treatment of knee OA by infiltrations of HA is moderately effective, that the effect obtained is similar to that provided by NSAIDs and superior to that of paracetamol, and that the efficacy of HA in the different studies could be slightly overestimated due to some biases in the studies [20].

A 2006 Cochrane review showed that there are certain differences between the different HA preparations depending on the assessment method and the time studied. The authors conclude that, in general, HA can be considered an effective and safe treatment for the treatment of OA, especially if the analysis is performed between 5 and 13 weeks post-infiltration. Efficacy can be maintained between 4 and 12 months depending on the preparation used [21].

More recently Bannuru., *et al.* have published a new meta-analysis comparing the effectiveness of the various treatments available for OA. The conclusions of the study showed that HA is the most effective of the treatments, with an effect size of 0.63 compared to 0.44 for ibuprofen or 0.18 for paracetamol [22].

### Structure Modifier Effect

Regardless of its efficacy for the relief of symptoms, the administration of HA seems to have biochemical properties beyond the simple lubrication and protection of the joint. The first evidence that HA could be considered a Disease-Modifying OA drug was provided by Smith and Ghosh when it was found that the administration of exogenous HA stimulated the synthesis of endogenous HA. In humans, the number of studies we have is limited. Listrat., *et al*. conducted a randomized, controlled pilot study of 36 patients with knee OA of the medial compartment. Patients who received three series of three injections of low molecular weight HA at three-month intervals showed less progression of the disease after one year of treatment, evaluated by arthroscopy, compared to controls, who received conventional treatment. An improvement in the quality of life and a reduction in the consumption of NSAIDs was also observed in the group treated with HA [23].

A group of 408 patients participated in a randomized study and received 3 cycles of 3 injections of low molecular weight HA or placebo and were evaluated radiographically after one year. The analysis showed no difference in the medial joint space between the two groups considering the total population of the study, but among the patients with less severe disease (joint space ≥ 4.6 mm) the subgroup treated with HA showed greater preservation of the joint space [24].

### Security Profile

Numerous clinical trials have been conducted to evaluate the safety profile of low and high molecular weight HA. In general, the side effects derived from its use described in the literature are rare and almost always transient. The most frequent adverse effects are local inflammatory reactions at the puncture site, pain and transient swelling of the knee. Post-infiltration arthritis has also been observed in patients previously affected by gout or chondrocalcinosis. Finally, a small number of allergic cutaneous and anaphylactic reactions have been reported [25].

## Discussion and Conclusion

### Are all the Hyaluronic Acids Equal?

The different preparations of HA available in the market differ in the molecular weight and its origin. We also differentiate between crosslinked and non-crosslinked HA. Regarding molecular weight, the conclusions we can draw from the different meta-analyzes are that in the short term, high-molecular-weight HA are more effective for relief, but after 6 months, intermediate molecular weight compounds are more effective. In 2005, Reichenbach and colleagues published a meta-analysis demonstrating that cross-linking did not provide great benefits and instead showed a greater number of side effects in these compounds [26].

The first HA were of animal extraction, specifically of avian origin. Subsequently, the HA of bacterial synthesis (Streptococcus equii) were developed. It is currently accepted that the seconds are safer since they cause a lower number of allergic reactions. In addition, bacterial synthesis HAs are synthesized at a lower cost.

### A New Concept: The Concentration of Hyaluronic Acid

There is evidence that the molecular weight and, to a greater degree, the concentration of HA directly influence the viscosity of the synovial fluid. Therefore, both physical characteristics, especially concentration, influence the behavior of HA.

Recently a study has shown that the lubrication of the joint depends on the synergism between different molecules. Two of the most involved molecules in this process are HA and Proteoglycan 4 (PRG4). The study confirms that the capacity of synergy between both molecules increases when the HA concentration increases [27].

### What is the pronolis® HD range: pronolis HD mono 2.5%, pronolis HD one 2.2%, pronolis HD mini 1.6% y pronolis Mini 1%?

Pronolis®HD is a class III medical device. It is a sterile viscoelastic solution of HA. The HA contained in Pronolis®HD is obtained by bacterial fermentation. It has a physiological molecular weight (between 1.2 - 3 MDa according to the concentration) and is available in a wide range of concentrations (1%, 1.6%, 2.2% and 2.5%), which allows a stepped and individualized treatment of the patient. In fact, Pronolis®HD is the viscosupplement with the highest concentration of HA currently available in the market.

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