

A Unifying Framework for Understanding the Lubricating Properties and Clinical Efficacy of Injectable Hyaluronic Acid Therapies

Edward D. Bonnevie¹, Devis Galesso², Cynthia Secchieri², Lawrence J. Bonassar^{1,3}

¹Sibley School of Mechanical and Aerospace Engineering, Cornell University, Ithaca, NY, ²Fidia Farmaceutici, SpA, Padua, Italy, ³Meinig School of Biomedical Engineering, Cornell University, Ithaca, NY,

Disclosures: Edward Bonnevie (N), Devis Galesso (Employee – Fidia), Cynthia Secchieri (Employee – Fidia), Lawrence J. Bonassar (Consultant – Fidia)

INTRODUCTION: Hyaluronic acid (HA) injections have been a mainstay of arthritis treatment for decades. However, much controversy remains about their clinical efficacy and their potential mechanism of action. This approach to arthritis therapy is often called viscosupplementation, a term which is rooted in the extremely high viscosity of the injected solutions. This terminology also suggests a mechanical pathway of action and further implies that efficacy is dependent on viscosity. Notably, previous studies of the relationship between viscous properties of hyaluronic acid solutions and their clinical efficacy have not been definitive [1-3]. Recently, we developed an experimental and analytical framework to study high viscosity cartilage lubricants that exploits Stribeck-like behavior [4]. The goals of this study were to characterize commercially available HA products in terms of their rheological and lubricating properties in vitro and to determine the extent to which these mechanical parameters correlate with clinical efficacy of these products reported during previous clinical trials.

METHODS: Rheological properties of approved HA products (Monovisc[®], Synvisc[®], Supartz[®], Euflexxa[®], Hyalgan[®], and Hymovis[®]) were evaluated using a cone and plate rheometer to determine low shear rate dynamic viscosity (η), storage modulus (G') and loss modulus (G'') [4]. Lubrication studies were performed on 6 mm diameter articular cartilage cylinders harvested from the patellofemoral groove of neonatal bovines. As described previously [4,5], cartilage samples were mated against a polished glass flat counterface while bathed in lubricant baths consisting of the HA products described above, phosphate buffered saline, or 2 MDA dextran. Samples were compressed to 25% strain and allowed to depressurize for 1 hour resulting in average normal loads of 2.6 N (92 kPa normal stress), and the glass counterface was reciprocated at predetermined speeds ranging from 0.1 to 10 mm/s. Friction coefficients (μ) were recorded as the ratio of shear load to normal load measured by a biaxial load cell for $n = 4$ samples for each product listed as well as PBS. Friction coefficients were analyzed as a function of Sommerfeld number (S), which was calculated as a product of the sliding speed (v), dynamic viscosity, and contact width (a) divided by the normal load (F) ($S = v \eta a/F$). Additionally, friction as a function of S was fit to a Stribeck-like model (i.e. elastoviscous transition curve) as reported previously [4]. This mapping was performed two way: first, using the measured viscosities to calculate values of S for each material; and second by considering viscosity to be a free variable and minimizing the RMS error between the measured friction data for each HA product and the model, which enabled the calculation of an effective lubricating viscosity (η_{eff}).

To determine the extent to which the measured rheological and tribological properties were correlated with clinical outcomes, data from clinical trials of each of the HA products was surveyed. For each product as well as placebo, the maximum improvement in WOMAC score was compared to η , G' , G'' , μ measured at 10 mm/s, and η_{eff} . Using all data on all products and data collected on PBS as placebo, linear correlation analysis was performed between the measurements listed and maximum improvement in WOMAC score.

RESULTS: HA products lubricated cartilage to varying degrees, but all reduced friction most effectively at high sliding speeds (Figure 1A). Profiles of friction as a function of Sommerfeld number calculated from measured viscosity indicated that cartilage samples lubricated in PBS appeared to be primarily in boundary mode, with HA products primarily achieving mixed mode lubrication, with some achieving minimum friction (Figure 1B). Calculating the effective lubricating viscosity for each HA product enabled calculation of a master elastoviscous transition curve, with a median RMS of 8.9% (Figure 1C). Standard measurements of HA rheology (η , G' , G'') were poorly correlated with maximum improvement in WOMAC score (R^2 from 0.12 to 0.25, see Table 1). However, tribological measurements were predictive of maximum improvement in WOMAC score, with friction coefficient negatively correlated with WOMAC score ($R^2 = 0.77$, Figure 2A) and $\log(\eta_{\text{eff}})$ correlated with WOMAC score ($R^2 = 0.78$, Figure 2B).

DISCUSSION: This study characterized the rheological and tribological properties of six commercial HA products used for osteoarthritis therapy. The lubricating action of all of these formulations on cartilage was well described by a Stribeck-like elastoviscous transition (Figure 1C) [4]. Analysis of this master curve (Fig 1C) allowed calculation of an effective viscosity that differed from measured viscosities to varying degrees. We show here that standard rheometry does not fully capture lubricating ability, which is consistent with recent evidence suggesting HA interacts with the articular surface in multiple ways [5]. Additionally, we found the strongest correlation between friction-based parameters (μ and η_{eff}) and changes in WOMAC. This finding suggests that viscosity alone is not a particularly strong predictor of pain reduction. This approach offers a novel method to evaluate potential clinical efficacy of viscosupplements that is more sensitive than rheological measurements alone.

SIGNIFICANCE: This study demonstrated that the lubricating action of several HA products can be understood using the framework of an elastoviscous transition and that this framework yields parameters that correlate well with clinical performance of these HA formulations. .

REFERENCES: 1) Altman+ *Am J Sports Med*, 2015; 2) Maheu+ *Clin Exp Rheum*, 2011; 3) Vitanzo+ *Am J Orthop* 2006; Bonnevie+ *PLoS ONE* 2015; Das+ *Biomacromolecules*, 2013

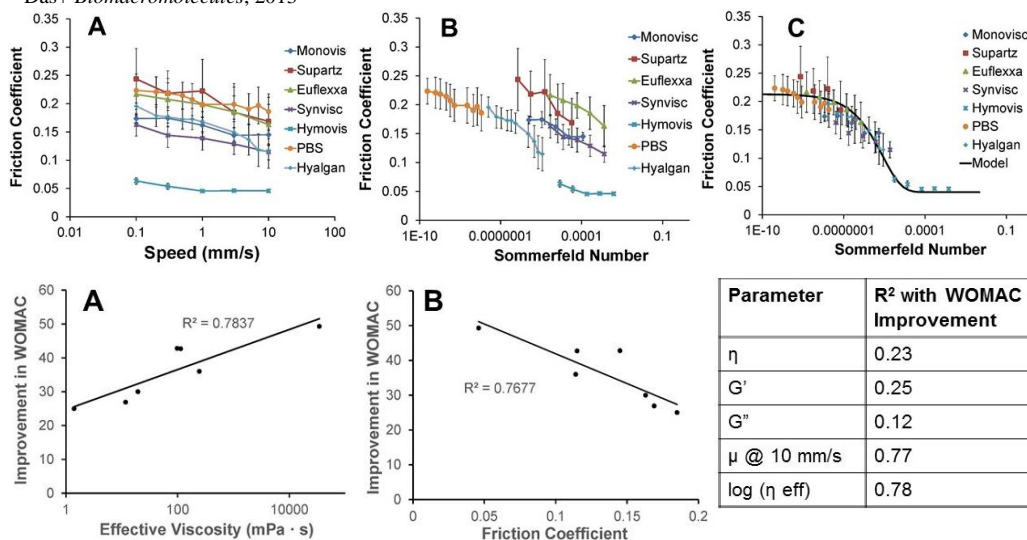


Figure 1: Comparison of friction coefficients for HA products as a function of speed (A) and Sommerfeld number (B) using measured viscosities. Fitting data to elastoviscous transition curve for a model lubricant enabled calculation of effective lubricating viscosities that collapsed all data sets onto a single curve. (n = 4)

Figure 2: Effective lubricating viscosity (A) and friction coefficient (B) are correlated with improvement in WOMAC scores reported in outcomes of clinical trials.

Table 1: Summary of correlation coefficients for comparisons of HA rheology and tribology with WOMAC score improvement