

Chronic Knee Effusions in Patients With Advanced Osteoarthritis

Implications for Functional Outcome of Viscosupplementation

David D. Waddell, MD
Andrew A. Marino, PhD

ABSTRACT: Intra-articular injection of exogenous hyaluronan (viscosupplementation) is an effective treatment for knee pain due to osteoarthritis, but the amount of dilution of the viscosupplement by the synovial fluid, which could affect efficacy, has not been previously considered. In this study, the synovial fluid volume was measured in patients with advanced osteoarthritis and the variation in viscosupplement concentration that would have occurred had the patients received that treatment was calculated. A closed aspiration was performed under anesthesia in this consecutive, prospective series of patients undergoing total joint arthroplasty for advanced osteoarthritis. Any remaining synovial fluid

was collected by means of open aspiration following an arthrotomy. Overall, 27.0 ± 15.5 mL (range: 10-70 mL) of synovial fluid was present in the joints. Irrespective of the particular proprietary hyaluronan product, the viscosupplement concentration would have varied by an approximate factor of 6. Interpatient variation in volume of synovial fluid may explain some of the observed variations in efficacy in patients treated with viscosupplementation. Stricter attention to the possibility of a joint effusion and aspiration of the joint where indicated might lead to improved results.

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INTRODUCTION

The prevalence of osteoarthritis increases with age throughout the elderly years⁵ and commonly involves the knee. First-line treatments include acetaminophen for chronic pain, weight reduction, topicals, and exercise. Nonsteroidal anti-inflammatory agents frequently are used to relieve pain, but they have drawbacks, particularly gastrointestinal irritation. Cyclooxygenase-2 inhibitors are alternatives, but they also are associated with side effects. Corticosteroid therapy and total knee replacement usually

are reserved for patients with severe disease when other therapies have failed. Injection of the knee with hyaluronan (viscosupplementation) is an alternative for patients who have not had success with basic analgesics, are not surgical candidates, or want to delay surgery.⁴

Although viscosupplementation can provide relief of knee pain due to osteoarthritis, wide inter- and intratrial variations in therapeutic efficacy have been reported.^{6,17} The variability in outcome success may have been due to the extent of the disease, the viscosity or elasticity of the hyaluronan products, injection technique, or any combination of these or other factors. Another possible and previously unconsidered explanation is dilution of the viscosupplement by the synovial fluid.

Prior to addressing this question directly in a clinical study, we thought it worthwhile to first assess whether any evidence to support the hypothesis exists. The objective of this study was to measure the volume of synovial fluid in pa-

Dr Waddell is from Orthopedic Specialists of Louisiana and Drs Waddell and Marino are from the Department of Orthopedic Surgery and Dr Marino is from the Department of Cellular Biology and Anatomy, Louisiana State University Health Sciences Center, Shreveport, La.

Correspondence: Andrew A. Marino, PhD, Louisiana State University Health Sciences Center, PO Box 33932, Shreveport, LA 71130-3932.

TABLE

PERTINENT LABEL DATA OF FOUR VISCOSUPPLEMENTS* APPROVED BY THE US FOOD AND DRUG ADMINISTRATION FOR TREATMENT OF KNEE PAIN DUE TO OSTEOARTHRITIS

Viscosupplement	Concentration (mg/mL)	Injection Volume (mL)	Dose (mg)	Molecular Weight (MDa)
Orthovisc	15	2.0	30	1.0-2.9
Supartz	10	2.5	25	0.6-1.2
Hyalgan	10	2.0	20	0.5-0.7
Synvisc	8	2.0	16	6.0

*Orthovisc, Ortho Biotech Products, Bridgewater, NJ; Supartz (Artz), Smith & Nephew, Memphis, Tenn; Hyalgan, Fidia, Turin, Italy; and Synvisc, Genzyme Biosurgery, Ridgefield, NJ

that it partially restored the viscoelasticity of synovial fluid that had decreased due to disease-related changes in the endogenous hyaluronan in the synovial fluid.² The viscosity of synovial fluid is a complex function of the hyaluronan molecular weight and concentration^{1,2} but, in general, changes of 0.5-1.0 mg/mL can affect viscoelasticity. Subsequent work suggested that the therapeutic efficacy of viscosupplementation was partly related to signaling of hyaluronan through receptors on synovial cells such as CD44.¹¹ Signaling by an agent is directly dependent on its concentration. Consequently, irrespective of whether the clinical effects of exogenous hyaluronan have a physiochemical or physiological basis, the variation in efficacy following intra-articular injection of hyaluronan might be at least partially explained by the dilution hypothesis because both modes of action are concentration-dependent.

Intra-articular injection of steroids produced a rapid improvement in symptoms (1-2 weeks), but efficacy decreased with time; viscosupplementation, in contrast, had a slower onset of efficacy but a greater improvement ($P < .05$) at 12-26 weeks.³ However, the influence of effusion on efficacy (for both treatments) is not well understood. The product labels for viscosupplements recommend that any joint effusion be removed before injection of the product.¹²⁻¹⁵ Effusions are sometimes aspirated prior to viscosupplementation, but clinical practices regarding identification and aspiration of an effusion vary widely. For example, in 17 prospective controlled clinical studies,¹⁷ the authors of 5 studies did not comment on whether they had aspirated the joints. In the remaining 12 studies, all patients were aspirated in 3 studies and variable numbers of patients were aspirated in the remaining 9 studies. It appears that joint aspiration was a significant uncontrolled factor that could explain at least part of the observed variability in treatment efficacy.

The extent of the variation in the volume of synovial fluid in the knee of patients with grade IV osteoarthritis supported the hypothesis that variability in response to viscosupplementation results at least partially from its dilution by the synovial fluid in the joint thereby justifying a

direct, prospective clinical study. In the meantime, stricter attention to the possibility of an effusion and aspiration of the joint where indicated might lead to improved results in joints injected with a viscosupplement.

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