Viscosupplementation with hylan G-F 20 in patients with osteoarthrosis of the knee

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***Abstract*:** Viscosupplementation (VIS) is one of several treatment modalities for osteoarthritis of the knee. It is useful in the treatment of osteoarthritis when other methods of conservative care have failed and it may be a safer method of treatment than oral chemical therapy which can have significant side effects with even short-term usage. The biochemical effects of hyaluronic acid are incompletely understood, however there are several accepted modes of action which result in a positive clinical effect on the function of the knee joint. There is some evidence that hyaluronic acid preparations with a higher molecular weight may be more beneficial to the patient. It is commonly used after arthroscopic meniscectomy and or debridement of the knee in a patient with chondral disease. The clinical effects have been well documented in multiple studies in patients with mild to moderate osteoarthritis in study groups before or after arthroscopic surgery of the knee. Adverse events do occur and are easily treated with only rare case reports of systemic effects. Furthermore, there is some evidence that VIS can prolong the need for total knee arthroplasty in the older patient as well.

***Keywords*:** knee osteoarthritis, postarthroscopy, viscosupplementation

Introduction

Viscosupplementation (VIS) is a common treatment modality for osteoarthritis (OA) of the knee. It has been used internationally for over 20 years when conservative care has failed [Sanofiaventis, 2007; Seikagaku, 2007; Ferring Pharmaceuticals, 2006; Genzyme Biosurgery, 2006; Anika Therapeutics, 2005; Scientific Group WHO, 2003; Centers for Disease Control and Prevention, 2001]. VIS has also been used in the treatment of OA of the shoulder, hip, ankle and elbow but its usage is limited to 'off-label' status in the United States in these joints. VIS has been supported by multiple clinical trials and its efficacy by several meta-analyses [Raman *et al.* 2008; Kirchner and Marshall, 2006; Waddell and Bricker, 2006a; Clarke *et al.* 2005; Kemper *et al.* 2005; Caborn *et al.* 2004; Kahan *et al.* 2003; Neustadt, 2003; Raynaud *et al.* 2002; Evanich et al. 2001; Huskisson and Donnelly, 1999; Wobig *et al.* 1999; Altman and Moskowitz, 1998; Wobig *et al.* 1998; Lussier *et al.* 1996; Carrabba *et al.* 1995; Scale *et al.* 1994; Dougados *et al.* 1993; Grecomoro et al. 1987]. Hyaluronan has many distinct biophysical, biochemical and cell regulatory functions. Hyaluronan is registered with the US Food and Drug Administration (FDA) as a device, but it is also a biologically active molecule. In this paper we review the biochemical effects of hyaluronan, its mechanism of action as well as it clinical performance in patients with OA of the knee.

Biochemical effects of hyaluronan

Hyaluronan is a highly coiled molecule at rest, such that when a force is rapidly applied to the molecule, it cannot uncoil and acts as an elastic body. If a direct force is applied slowly, for example when walking, the molecule then unwinds and acts as a viscous lubricant. This property is critical for resisting compressive forces and reducing friction between opposing surfaces of cartilage and depends on the presence of a physiologic concentration of hyaluronan in the synovial fluid. Initially these rheological properties were believed to be the primary mechanism by which hyaluronan therapy was beneficial in treating pain from OA. The biochemical effects of hyaluronan include inhibition of tissue nociceptors, stimulation of endogenous hyaluronan, anti-inflammatory effects and inhibition of metalloproteinase (MMP) activity [Belmonte *et al.* 1998; Moore and Willoughby, 1995]. Furthermore, increased production of endogenous hyaluronan has

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recently been shown in which concentrations of hyaluronan were measured in knee aspirates at the time of VIS injection and at 3 and 6 months following injection [Bagga *et al.* 2006]. Although the positive clinical effect of therapy can last from 6–12 months after initial treatment, Waddell and colleagues showed a mean time to the second course of hylan G-F 20 of 19 months in 70 patients [Waddell *et al.* 2003].

Another biochemical effect noted by Marino and colleagues was a significant reduction in MMP activity after interleukin 1β stimulation [Marino et al. 2004]. Both native hyaluronan and hylan G-F 20 were shown to inhibit MMP activity when their concentrations exceeded 2 mg/ml. Higher molecular weight substances such as hylan G-F 20 were shown to be more effective in producing this effect. By showing an ability to inhibit MMP activity, this study raised the possibility of the disease-modifying capability of VIS, although further studies will be necessary to confirm this theory.

Clinical effects of hyaluronan

The clinical effects of VIS showed that hyaluronan was more effective in patients aged <65 years and in those with less-advanced disease [Wang *et al.* 2004]. Furthermore, some authors have concluded that a chemically cross-linked product may be more clinically effective [Lo *et al.* 2004]. A Cochrane review of randomized, controlled trials of all hyaluronan formulations has confirmed the efficacy and safety of the hyaluronan class of therapies [Bellamy *et al.* 2006]. Treatment paradigms including VIS have been proposed over a decade ago that consist of nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 inhibitors, analgesics, physical therapy, intra-articular steroids and arthroscopic surgery. In patients with symptomatic OA, pain can still persist after arthroscopic meniscectomy and debridement of chondral lesions commonly noted in patients at the time of arthroscopy [Bin *et al.* 2008]. Marshall and colleagues reported the use of intra-articular hylan G-F 20 in patients with continuing pain after arthroscopic debridement (Table 1) [Marshall *et al.* 1996]. Most of these patients had severe OA. Chen and colleagues reported a level I study on 77 patients with OA receiving VIS after knee arthroscopy [Chen *et al.* 2002]. The knee muscle strength index and patient visual analog scale (VAS) pain scores were statistically better in the VIS group. Hempfling reported the results of a level I study in 80 patients undergoing arthroscopic joint lavage with and without hyaluronan postoperatively [Hempfling, 2007]. Both the control and the study groups had positive effects at 3 months, but the treatment effect was maintained in the VIS group for up to 1 year. Zietz and Selesnick reported a small-group level I study of patients that were treated with hylan G-F 20 at a mean initiation of treatment of 3.4 months after arthroscopy [Zietz and Selesnick, 2008]. Western Ontario and McMaster University (WOMAC) score and International Knee Documentation Committee (IKDC) score were significantly improved at baseline, 3 and 6 months postoperatively compared with scores before arthroscopy. The authors also reported improved activity levels associated with hylan G-F 20 administration at 3 months follow up. Huskin and colleagues

Table 1. Clinical effects of hyaluronan and recent studies.

Study	Type of study	Findings
Marshall *et al.* [1996]	Meta-analysis	68% with severe OA did not progress to TKA S/P tx
Chen *et al.* [2002]	Level I study: hyaluronan S/P scope	VAS scores increased in hyaluronan patients
Dai *et al.* [2002]	Level I study: hyaluronan S/P scope	VAS scores increased in control group
Rolf *et al.* [2005]	Level I study: hyaluronan *vs* placebo	Improved with hyaluronan and hylan
Mathies [2006]	Viscoseal S/P meniscectomy	Decreased effusion and pain
Hempfling [2007]	Level I study: hyaluronan *vs* control	Decreased pain up to 1 year
Ulucay *et al.* [2007]	Level I study: hylan G-F 20, Orthovisc, Adant, and S/P scope	Increased results
Huang *et al.* [2007]	Level I study: hyaluronan S/P anterior cruciate ligament repair *vs* saline solution	Hyaluronan increased results
Zietz and Selesnick [2008]	Level I multicenter study	Increased VAS scores S/P scope for OA

VAS, visual analog scale; OA, osteoarthritis; TKA, total knee arthroplasty; S/P, status post; tx, treatment.

reported in a level I study in knees with 84% level I chondromalacia of the patella and 40% had grade II medial and lateral femoral condylar changes [Huskin *et al.* 2008]. Significant improvement in VAS pain scores was noted while walking. WOMAC scores, physician global assessment, and patient assessment all showed statistically significant positive results at all other time points in patients with symptomatic OA subsequent to arthroscopic intervention followed by VIS treatment.

The recent usage of 'Synvisc One' which consists of a 6 ml injection of hylan G-F 20 comparing it with a placebo in patients with symptomatic knee osteoarthritis has been reported by Chevalier [2009]. In this level II study, 253 patients with Kellgren Lawrence grade II or III X-ray findings were randomly assigned and the patients receiving hylan G-F 20 experienced statistically significant greater improvements in WOMAC A pain scores and several of the secondary outcome measures than patients receiving placebo over 26 weeks.

Several studies of VIS have confirmed the benefit of treatment with more than one course of VIS. Most patients receiving a second course of therapy have been shown to experience continued pain relief for up to 6 and 12 months after therapy [Waddell *et al.* 2003, 2005]. In another study, Raynaud reported that a second course of therapy with hylan G-F 20 was just as effective as the first course in a study comparing intra-articular hyaluronan with conservative care [Raynaud, 2005]. Kolarz and colleagues reported long-term improvement in a small group of patients with OA with repetitive injections every 6 months [Kolarz *et al.* 2003].

VIS products are well tolerated and are associated with a low incidence of local adverse events. Since the vast majority of products on the market are avian derived, occasionally systemic hypersensitivity reactions may occur. The typical adverse event seen in patients receiving intra-articular hyaluronan products is pain and/or swelling of the injected joint. These local adverse reactions are easily reversed with joint aspiration, injection of steroids or administration of oral steroids [Waddell, 2007]. In contrast, self-limited synovitis has been reported in about 2% of cases of intra-articular injections with corticosteroids [Gray and Gottlieb, 1983]. Local adverse events may increase slightly with more than one course of hylan G-F 20 [Waddell and Bricker, 2006b].

Discussion

VIS has been accepted by the American Academy of Orthopedic Surgeons (AAOS), American Pain Society and American College of Rheumatology, Medicare and the vast majority of private payers as a treatment modality for the patient with knee osteoarthritis. In December 2008, the clinical guidelines reported by the AAOS upon a review of nonarthroplasty treatment options for knee OA, stated that 'we cannot recommend for or against the use of intra-articular hyaluronic acid for patients with mild to moderate symptomatic OA of the knee'. This was despite a review of level I and level II published articles and their grade of recommendation was 'inconclusive' [American Academy of Orthopedic Surgeons, 2008]. The efficacy of intra-articular hyaluronan is comparable to or greater than that of therapies such as NSAIDs without the serious systemic adverse effects which can occur after taking even a short course of NSAIDs. Clinical studies have also demonstrated that the efficacy of VIS is similar to or better than that of conventional treatment, intra-articular steroids, arthroscopic lavage, physical therapy or exercise [Waddell, 2007]. Accumulating evidence also confirms that multiple courses of VIS are effective in maintaining OA pain relief and may also decrease the usage of NSAIDs. It appears that the majority of clinical trial data indicate that the higher the molecular weight of the intra-articular hyaluronan product, the greater the treatment effect and the longer its duration of action for a given number of injections [Waddell and Bricker, 2006a]. Treatment with VIS is associated with a low incidence of local adverse events and few systemic adverse events. All VIS formulations are very well tolerated in comparison to NSAID therapy and reactions are typically benign and transient. VIS may also delay total knee arthroplasty (TKA) which may reduce the need for revision surgery especially in younger patients [Waddell and Bricker, 2007; Burns *et al.* 2006]. VIS is an important conservative treatment modality in the care and treatment of patients with OA of the knee and certainly may be helpful in other joints as has been noted outside the United States. Further biochemical research as well as prospective, randomized clinical level I and level II studies need to be performed to confirm the efficacy of this chemical treatment modality.

Conflict of interest statement

The authors are both consultants to Genzyme Biosurgery, Cambridge, MA but report no conflict of interest.

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