A comparison of the functional efficacy of osteoarthritic knee joints following viscosupplementation treatment

Stephanie Beasley Buford
University of Nevada, Las Vegas

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A COMPARISON OF THE FUNCTIONAL EFFICACY OF OSTEOARTHRITIC KNEE JOINTS FOLLOWING VISCOSPPLEMENTATION TREATMENT

by

Stephanie Beasley Buford

Bachelor of Science
Oklahoma State University
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Master of Science in Kinesiology

Suzanne Pero
Examination Committee Chair

Dean of the Graduate College

M.A. Clay
Examination Committee Member

Richard D. Cundy
Examination Committee Member

Susan S. M. Smith
Graduate College Faculty Representative

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ABSTRACT

A Comparison of the Functional Efficacy of Osteoarthritic Knee Joints Following Viscosupplementation Treatment

by

Stephanie Beasley Buford

Dr. Suzanne Pero, Examination Committee Chair
Assistant Professor of Kinesiology
University of Nevada, Las Vegas

The purpose of this study was to compare two viscosupplementation products, Hyalgan and Synvisc, that may be used to treat osteoarthritis (OA) of the knee. Hyalgan and Synvisc, have both been studied extensively against NSAIDS and placebos and have both yielded significantly greater improvements in reducing the symptoms associated with OA. Forty - one patients diagnosed with OA of the knee volunteered to participate in this study. Each patient received the standard protocol of lateral injections with extended knee of 2 ml of either Hyalgan or Synvisc using a 20 gauge needle. Product efficacy and functional outcome were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and was administered to every participant prior to their first injection and again at two and four months post final injection. The results suggest that both viscosupplementation products are comparably effective in decreasing pain and stiffness, and increasing daily function.
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DEDICATIONS

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CHAPTER 1

INTRODUCTION

Osteoarthritis (OA) is the most commonly occurring form of arthritis in diarthrotic joints, such as the knee. Clinical studies have concluded that OA affects millions of Americans and is one of the leading causes of disability in the elderly (Clyman & Pompei, 1996; Harris, 1993; Dieppe, Frankel, & Toth, 1993; Simon, 1999). OA is often idiopathic and results in both mechanical and biological defects that affect all tissues of the joint cavity. Physiologically, OA is characterized primarily by the degeneration of hyaline cartilage, subchondral sclerosis, formation of osteophytes, decreased synovia or increased synovia with decreased viscosity, and a multitude of other pathologies (Goorman, Watanabe, Miller, & Perry, 2000; Wright, Maurer, & Di Cesare, 2000). Physically, OA is accompanied by joint pain, tenderness, limited range of motion (ROM), crepitus, and minor inflammation (Adams, Atkinson, Lussier, Schultz, Wade, & Zummer, 1995; Creaamer & Hochberg, 1997). In addition, there is a degradation process in the articulating surfaces of the joint associated with OA which appears to be irreversible in a cycle-like progression.

The cycle is usually initiated by repetitive activity occurring over time which has resulted in wear and tear or microtrauma to the joint. Synovial fluid is found inside the
joint space and in the articular (hyaline) cartilage covering the femur and the tibia. In healthy diarthrotic joints, synovial fluid is viscous with elastic properties. The wear and tear to the joint associated with OA leads to the dilution of synovial fluid. The dilution of synovial fluid results in decreased viscosity and elasticity. This decrease results in increased friction between the tissues located within the joint space which stimulates the nociceptors (nerves in charge of transmitting pain to the central nervous system - CNS) of the joint capsule resulting in the patient's pain and loss of movement and/or function.

Upon restriction of mechanical movement, there is a decrease in the production of synovial fluid. The actual movement of synovial fluid within the joint capsule during activity initiates the production of additional fluid. With decreased movement associated with pain, there is a decrease in fluid production resulting in the dilution of the synovial fluid. This is the beginning of the cycle of OA progression (Uebelhart & Williams, 1999).

A number of byproducts associated with the inflammatory process may also influence the production of synovial fluid. Inflammation produces certain chemicals that retard the stimulation of synovial fluid production which decreases the ability of the fluid to saturate the joint capsule.

Hyaluronic acid (HA), a type of polysaccharide found in synovial fluid, has recently become the focus of treatment for OA. Synovial fluid has many functions in the knee such as lubrication, shock absorption, nutrition, cell "traffic controlling", and protection for nerve endings such as the nociceptors. (Peyron, 1993). The two most prominent functions of synovial fluid associated with patient comfort include lubrication and shock absorption. The efficacy of lubrication and shock absorption is a direct result of the viscoelasticity of
synovial fluid. The viscoelasticity of synovial fluid is dependent on its HA content. HA is found to be deficient in the synovial fluid and in surrounding tissues of OA affected joints. This deficiency, again, initiates the cycle. With less movement there is a decreased stimulation of HA production. The patients' chief complaint is primarily pain which is often described as debilitating, resulting in a decrease or cessation of activity. This decrease or curtailment in activity significantly and directly contributes to the decrease in viscosity and production of synovial fluid.

The most common treatments of osteoarthritis include: physical therapy, corticosteroidal injections, saline lavage, total knee replacement, glucosamine, analgesics, and nonsteroidal anti-inflammatories (NSAIDS). There are complications and limitations with each of these options (Creamer & Hochberg, 1997; Dieppe et al., 1993; Harris, 1993; Wen, 2000; Goorman et al., 2000; Wright et al., 2000; Uebelhart & Williams, 1999). Physical therapy can be costly for the patient due to minimal authorization by insurance companies. Corticosteroidal injections may only be administered on an intermittent basis and may be associated with cartilage destruction and synovitis. Saline lavage has rarely been used due to the documentation that it is only minimally effective. Total knee replacement is not normally an option except in extreme and desperate cases considering the magnitude of the surgery involved, the average age of the patients, lengthy rehabilitation, and insurance limitations. Glucosamine is a dietary supplement that has not been FDA approved or widely researched. The two most popular choices for osteoarthritic treatment are oral analgesics and non steroidal anti-inflammatory drugs (NSAIDs), with the latter being the most common. Some of the concerns that have arisen
with the utilization of NSAIDs include the fact that OA generally has a low inflammatory component and that the cost for these drugs averages approximately $55 per month. In addition, NSAIDs have documented toxic characteristics that may result in gastrointestinal problems such as ulcers and bleeding (Wu, Shih, Hsu, & Chen, 1997; Creamer & Hochberg, 1997; Adams, 1993; Adams, Atkinson, Andre, Lussier, Siminovitch, Wade, & Zummer, 1998; Simon, 1999).

As a result of these problems, physicians and researchers began investigating other more efficient and practical forms of treatment. In the early 1960’s, a concept termed viscosupplementation was developed. The theory behind viscosupplementation was to replace the missing hyaluronan (HA) by injecting a hyaluronan-like substance directly into the affected joint. When this concept first surfaced, it was used only in European countries in joints of horses and then a few years later it was used for human eye surgery. In 1987, Europeans initiated viscosupplementation use for human joints and in 1997 the FDA approved its use in the U.S. but only in knee joints. Two products are now being widely utilized as well as researched extensively. These products, Hyalgan and Synvisc, are very different in molecular weight, viscosity, and administration protocol. However, both products are made from a hyaluronan base and are injected directly into the affected joint capsule. The ultimate goal for each product is the same, to decrease the pain and stiffness in arthritic joints resulting in increased activity levels for patients. Both products have been clinically proven to accomplish this task more effectively and efficiently than the alternative forms of treatment. Most studies support the efficacy of Hyalgan and Synvisc
when compared to other treatments and to placebos. Currently, however, there are no published studies that compare the efficacy of Hyalgan and Synvisc to each other.

Furthermore, the results from previous studies have revealed that each product demonstrates a potential downfall which may detract patients from choosing viscosupplementation as a treatment choice, especially when only one treatment product option was given. There have been some reports of injection site pain and swelling associated with the use of Synvisc which has a significantly higher molecular weight than Hyalgan (4 to 6 million daltons vs. 500,000 to 700,000 daltons respectively). The pain resulting from the injections may contribute to patients not returning for subsequent injections to complete the treatment protocol. Due to Hyalgan’s lower molecular weight, the administration protocol consists of five intrarticular injections over a five week period as compared to Synvisc’s three injections during a three week period. The fact that five injections are required for the Hyalgan protocol may deter some patients from exploring it as a treatment option.

The purpose of this study is to compare the functional efficacy of Synvisc to Hyalgan to determine if either viscosupplementation product is more effective at decreasing pain and stiffness and improving the functional activity levels of patients suffering from OA of the knee. While it is widely accepted that both Hyalgan and Synvisc are effective in alleviating the symptoms of OA, it is crucial to note that viscosupplements are attempting to treat the underlying cause of OA and not just the symptoms as is the case with the other available osteoarthritis treatment protocols. However, due to the reports of adverse
affects associated with the different products, the information obtained in this study may be crucial in determining the most effective course of treatment for each patient.
CHAPTER 2

LITERATURE REVIEW

Brief Anatomy and Physiology of the Knee Joint

The tibiofemoral joint (knee joint) is the largest and one of the most complex joints in the body (Pfeiffer & Mangus, 1995; Magee, 1987). The knee is considered a modified hinge joint or a trochoginglymus joint because not only can it perform extension and flexion movements but rotational movements as well (Thompson & Floyd, 1994). There are several components responsible for the complexity of the knee joint. The femur and the tibia articulate to form the major portion of the joint. These bones are held together and stabilized by several ligaments, primarily the cruciate and collateral ligaments. The space between the tibia and the femur is filled by two menisci, often referred to as articular discs, that provide lubrication, nourishment, and cushioning for the joint. The patella (knee cap) is a sesamoid bone that is completely encapsulated by the quadriceps tendon and articulates with the femur but not with the tibia (Pfeiffer & Mangus, 1995). Bursae and fat pads are also found within the knee joint and serve to cushion and protect the articulating surfaces during movement and weight bearing activities. The synovium is a lining that lies beneath the patella between the tibia and femur creating a sac which
encapsulates all the components of the knee joint except for the cruciate ligaments (Thompson & Floyd, 1994; Hertling & Kessler, 1996). The synovial sac contains synovial fluid which is extremely important for the health of the joint components due to its viscoelastic components. This viscoelastic characteristic of synovial fluid is highly dependent upon the content of a certain polysaccharide called hyaluronic acid (HA) (Mensitieri, Ambrosio, Iannace, Nicholais, & Perbellini, 1995). In normal, healthy joints the viscosity of the synovial fluid provides lubrication, shock absorption and nutrition to the articular cartilage and joint surfaces. Without the viscous synovial fluid, the joint surfaces begin to wear creating joint inflammations, injury, trauma, pain, and disturbing proper joint function (Wu, Shih, Hsu, & Chen. 1997). In the normal knee, there is approximately 2.5-3.5 mg/ml of hylauronan with a molecular weight of 4-5 million daltons. In the osteoarthritic knee, there is approximately .8-2 mg/ml of hyaluronan with a molecular weight of about 4 to 5 million daltons.

Osteoarthritis

Osteoarthritic diseases are a result of mechanical, biological, biochemical, and enzymatical processes (Creamer & Hochberg, 1997; Harris, 1993; Clyman & Pompei, 1996). Osteoarthritis (OA) is physiologically characterized by deterioration and loss of articular cartilage, subchondral sclerosis, osteophyte formation, inflammation of the synovium and deterioration of the supporting structures of the joint. (Adams, 1993; Goorman, Wantanabe, Miller, & Perry, 2000; Wright, Maurer, & Di Cesare, 2000). OA is the most common form of articular cartilage degeneration. Its prevalence generally
increases with age and physical activity (Wu, Shih, Hsu, & Chen, 1997). Cartilage damage in OA is likely due to the release of enzymes from the chondrocytes into the matrix which lead to additional cartilage matrix degradation. With cartilage damage, fragments of collagen, proteoglycan and other matrix components are released into the cartilage and synovial fluid (Simon, 1999). These may initiate or accelerate an inflammation reaction in the synovial membrane by acting as neoantigens or irritants. The inflammation in the membrane creates a cycle with additional cartilage being degraded and those degradation products provoking increased inflammation (Pelletier & Pelletier, 1993). Inflammation of the synovial membrane is often seen in a clinical setting as a painful, swollen and hot joint. Whether OA is related to physiological problems or normal mechanical wear and tear, the joint pain can cause limitations in a patient’s enjoyment of life. Patients experience pain with motion, gelling phenomenon, and crepitus. The most prominent symptom of OA is pain which is usually aching in nature and often poorly localized. In the early stages, the pain usually occurs in an active joint. However, there are many complaints of morning stiffness which is short-lived lasting between 15 and 30 minutes. Management of OA entails the use of drugs, physical measures and/or surgery. The goal of treatment is to treat the symptoms by relieving pain allowing the patient to be as active and independent as possible. Because OA has a mild component of synovial inflammation, the most commonly used medication for treatment are NSAIDs. Chronic NSAID therapy is associated with an increased risk of renal side effects, GI side effects including ulceration and bleeding, and negative effects concerning bone metabolism (Wu et al., 1997; Creamer & Hochberg, 1997; Adams, 1993; Adams, Atkinson, Andre, Lussier,
Schultz, Siminovitch, Wade & Zummer, 1995). Other analgesic agents that are used and
do not carry the GI or renal side effects are acetaminophen (600 mg bid) and
propoxyphene (100 mg qid) but these medications are usually only minimally effective.
Corticosteroids are also used but should not be injected more than four times per year
because there is some evidence of accelerated cartilage loss and bone atrophy.
Cryotherapy and thermotherapy may also be used to relieve symptoms. Physical therapy
and exercise programs attempt to decrease muscle atrophy and increase or maintain ROM.
Surgical intervention, including total knee replacement, is indicated for patients who have
limited function and intolerable pain (Harris, 1993; Wu et al., 1997). Osteoarthritis is the
most common form of articular cartilage degeneration. At the present time, no definite,
long term treatment exists for the majority of patients suffering from this disease. OA
effects nearly 16 million Americans and is one of the leading causes of disability in adults
over age 65 (Clyman & Pompei, 1996). Osteoarthritis of the knee is responsible for a
huge portion of suffering and disability that results in substantial health care expenditure
(Dieppe, Frankel & Toth, 1993).

Hyaluronic Acid and Synovial Fluid

In human arthritis, the elasticity and viscosity of the synovial fluid are much lower than
in the normal joint (Balazs & Denlinger, 1993; Goorman et al., 2000). Within the matrix
or ground substance that fills the space between cells of the knee joint is a substance called
hyaluronic acid. Hyaluronic acid (HA) is a long mucopolysaccharide (or
glycosaminoglycan) chain made up by repeating units of N-acetyl-D-glucosamine and D-
glucuronic acid (Balaz & Denlinger, 1993; Mensitieri et al., 1995). HA is plentiful in cartilage and synovial fluid, and is responsible for several actions: a lubricant and a shock absorber; an energy storing agent between the opposing cartilages; a selective molecular sieve; a cell traffic controlling agent; a viscoelastic shield around the synoviocytes and the adjacent nerve endings such as nociceptors. All these actions depend on the high viscoelasticity of the HA in normal joint fluid (Peyron. 1993; Adams et al., 1995; Simon, 1999; Goorman et al., 2000). HA is an important constituent of normal human synovial fluid and is both quantitatively and qualitatively abnormal in osteoarthritic knees. The performance of human articular joints is strictly connected with the viscoelastic properties of synovial fluid which determine load transmission, lubrication, wear inhibition and protections of the articular cartilage and soft tissue surfaces from mechanical stresses during joint function. The viscoelasticity of synovial fluid mainly depends on the concentration, molecular weight, and interactions with other molecules (Uebelhart & Williams, 1999). It has been reported that due to abnormal reactions in the synovial fluid, the HA concentration decreases in the course of OA. As a consequence of these reactions and modifications, the rheological properties of synovial fluid appear to be very different from those of normal ones. The reduction of synovial fluid viscoelasticity allows the cartilage to cartilage contact which results in an increase in surface wear and damage that ultimately causes pain, sometimes intolerable (Mensitieri, Ambrosio, Iannace & Nicolais, 1995; Listrat, Ayral, Patarnello, Bonvarlet, Simonnet, Amor & Dougados, 1997).

Hyaluronan serves as a primary isolating and lubricating agent. Most of the joint capsule of the knee is completely saturated within the hyaluronan molecular network. The primary
role of the hyaluronan molecular network is to surround and protect the surface collagen structure of the cartilage and synovial membrane. Hyaluronan is present in arthritic fluid but in a lower molecular weight form resulting in less effectiveness to the joint due to a decrease in molecular interaction and HA concentration as a result of dilution from exudation (Al-Assaf, Meadows, Phillips & Williams, 1996; Listrat et al., 1997)). In OA patients, the synovial fluid is more abundant and less viscous. The HA molecules are smaller and further apart, which decreases the rheological properties of the synovial fluid. The concentration of HA is decreased and the molecular weight is reduced (Peyron, 1993). Elastoviscosity of HA is extremely dependent on the shear forces to which it is exposed. At very low frequency, the solution is very viscous with decreased elastic properties. At higher frequency the solution is extremely elastic. This means that when external forces move these solutions slowly, they behave like viscous fluids and when movement is fast they behave like elastic bodies. The movement of the joint generates flow of synovial fluid that maintains a continuous exchange between the synovial fluid and the intercellular fluid of the joint tissues (Balazs & Denlinger, 1993; Pelletier & Pelletier, 1993). Diminished viscoelasticity of the synovial fluid alters the mechanical force transmission to the cartilage increasing its susceptibility to mechanical damage or wear and tear. In the normal knee joint, there is approximately 2 ml of synovial fluid, the molecular mass of hyaluronan is about 4 to 5 million daltons and the estimated total hyaluronan is between 4 to 8 mg.

HA is an extremely important component within the joint because it creates a thicker fluid consistency. This type of consistency gives the tissues a greater cushioning and
stability effect. HA gives the joint a "gel-like" environment. The lower the HA content, the more watery the encapsulation becomes resulting in a less stable environment with unnecessary movement and friction among tissues. This friction such as bone rubbing bone or cartilage is the cause of the debilitative pain for patients.

Viscosupplementation

Viscosupplementation is direct injection of a hyaluronan (HA) substance into the joint capsule of the OA affected joint. HA for this procedure is extracted from rooster combs, umbilical cords, or from bacterial cultures (Wright et al., 2000). The HA is separated from any pro-inflammatory, immunogenic, pyrogenic or chemotactic constituent, while preserving its polymerization. Its purpose is to increase the rheological properties of the joint not only aiding the joint but consequentially reducing the physical problems that become chief complaints of the patients. The concept of viscosupplementation as a therapeutic modality for treating arthritic pain was invented in the 1960's by E.A. Balazs and named by J.L. Denlinger in 1989. The first hyaluronan product was initially used to treat arthritis in horse joints and for humans as a viscosurgical product accompanying eye surgery. In 1987, viscosupplementation presented itself to the market as a treatment modality in human joints, mainly the knee. Very few studies so far have concentrated on any other human joints such as the hip or shoulder. Currently, the FDA has only approved viscosupplementation for use in the knee joint.

Pain and loss of function are the symptoms which generally lead patients to seek medical attention for osteoarthritis. At present, no medical or physical therapy has been
shown convincingly to affect the rate of the deterioration of the affected joint structures, so therapeutic efforts are rightly directed to symptomatic relief of pain and attempts to preserve joint function. Many types of treatments have a role in the management of the pain of OA. These include symptomatic pharmacological treatment with analgesics, NSAIDS, and intra-articular corticosteroid injections, muscle strengthening exercises, weight loss, the use of devices such as canes and orthodics, arthroscopic joint debridement, joint lavage, total joint replacement, education and counseling (Simon. 1999). While analgesics may be as effective as NSAIDs in treating some patients with OA of the knee, NSAIDs are considered a standard treatment for OA. Unfortunately, many patients either cannot tolerate NSAIDs or suffer serious side effects.

Viscosupplementation has been shown, mainly in European studies, to be a safe and efficient treatment of OA in the knee with very few side effects. (Adams et al.. 1995). Several injections are needed (from three to five depending on product) to achieve efficacy because the rheological properties are so inadequate in the affected knee that it takes a sufficient amount of product to restore the elasticity and viscosity of the synovial fluid in the joint. Another reason for multiple injections may be the body's inherent programming to rid the body of foreign substances, as the body may be eliminating the HA as it is injected. The importance of the molecular weight of the product may be crucial in this capacity. The results of viscosupplementation therapy might therefore be expected to depend upon the preparation of the HA product. Because of this limitation, hylans (chemically cross-linked hyaluronans) were developed to improve the efficacy of viscosupplementation. The purpose of hylan productions was to substantially increase the
rheological properties of the injected product beyond those of the defective synovial fluid and even above those of normal fluid (to compensate to dilution) and to increase the time of residence of the injected HA in the joint (Peyron, 1993). Cross-linking hyaluronan improves its utility for viscosupplementation in several ways. First, the rheological properties are increased; second, it has a longer retention time in the synovial space; and third, because of the cross-links, it becomes more resistant to free radical degradation (Balazs & Denlinger, 1993; Lussier et al., 1996). However, there has been some speculation that when using cross linking, the product becomes more "gel-like". This gel-like substance requires a larger needle for injection and there may be less fluidity in the joint which may enhance some injection site pain and other side effects that will be described later. Recommended procedures entail repeated injections which have been found to be necessary by all investigators to achieve a significant and lasting improvement regardless of the product preparation. Three weekly injections are a minimum. Results in practically every published study to date has stated that there is an increase in activity, functional ability and ROM and also a decrease in pain and stiffness with no major side effects that may last up to six months with no further injections. Studies report an increase in the concentration and molecular weight of HA in the synovial fluid several weeks after the last injection, pointing to a restoration of HA to near normal. Overall, the published studies that used a preparation of HA with a molecular weight of at least 500,000 - 750,000 daltons, were found to be effective.

Not all viscosupplementation products yield the same molecular weight. In fact, the two products being used in the United States vary greatly in molecular weight (Hyalgan at
500,000 daltons - 750,000 daltons and Synvisc at 4 - 5 million daltons). How important is molecular weight when comparing the efficacy of these two products? Aviad and Houpt (1994) addressed this question and found that the common perception was that higher molecular weight HA was superior to lower molecular weight HA. This theory was based on the idea that if lower molecular weight preparations of HA seem to enhance the factors that help restore the rheological properties of synovial fluid then higher molecular preparations will enhance this process to an even greater extent. However, they discovered in the literature that there is not much research to support this claim. Aviad and Houpt (1994) researched studies by two investigators that rejected the claim of high molecular weight HA raising viscosity of synovial fluid and HA concentration more so than lower weight HA. Aviad and Houpt researched a study by Hilbert et al., that compared joints injected with an HA preparation of 1 - 2 million daltons to a control group not injected at all. The findings were that the mean concentration did in fact increase from 1.05 mg/ml to 2.46 mg/ml but only lasted for 2 days. By day four, the concentration of the treated joints fell to pre-injection levels and there were no differences in subsequent days between the two groups. In other studies there are similar findings that high molecular weight HA injections do not cause the synovial membrane to synthesize high molecular weight HA inside the joint (Aviad & Houpt, 1994).

In addition to the studies comparing the efficacy of molecular weight in HA, a study by Puttick, Wade, Chalmers, Connell and Rangno (1995) researched the acute local reactions after viscosupplementation using the crosslinked product hylan GF - 20 (Synvisc). In this study, the authors used twenty-two patients with a mean age of 63. The recommended
injection protocol for Synvisc was followed (3 injections of 2 ml at weekly intervals). A total of 88 injections were administered to 28 knees. Ten injections were associated with reactions such as pain, swelling and warmth, some lasting up to 3 weeks. Four of the patients had local reactions so severe that there was an increased difficulty in movement. The synovial fluid of the negatively affected patients was effused and analyzed in an attempt to determine the underlying cause of the adverse reaction. The results showed elevated white cell counts with negative cultures and crystal examinations. The fluid, in some cases, was yellow and cloudy which was not found prior to injection. This research resulted in more than one quarter of the patients experiencing adverse effects to the higher molecular weight HA. The authors add that the reactions they noted appeared to have been directly related to hylan (the cross linked product hylan GF-20). Although there were adverse reactions found, most patients did experience an increase in ROM, a decrease in pain and stiffness allowing for increased activity level, and a decreased amount of unpleasant side effects compared to other forms of treatment.

After researching three reported cases of calcium pyrophosphate dihydrate (CPPD) crystals found in knee joints immediately following treatment of OA with Synvisc, Kroesen, Schmid, and Theiler (2000) report a fourth case. This case report describes a 60 year old man who was diagnosed with OA in both knees. There was no history of crystal arthropathy, no documented signs of cartilage calcification, and no family history of CPPD arthritis. Kroesen et al. (2000) also document that the patient had no form of CPPD associated diseases such as haemochromatosis, hyperparathyroidism, hypophosphatasia, hypocalcaemia, hypomagnesaemia or hypothyrosis. Treatment protocol for Synvisc is one
injection every week for three weeks. The patient tolerated the first injection very well but then two days following the second injection a week later, the man developed very painful swelling, redness and the loss of function of his right knee. The results of many tests revealed no other indications other than the presence of rhomboid crystals that were defined as CPPD crystals. The patient was treated with NSAIDS and a steroid injection and within a few days, the symptoms totally disappeared. Viscosupplementation treatment was not resumed.

In studies researching the efficacy of sodium hyaluronate (for example Hyalgan), a category concerning the prevalence of adverse reactions due to injection was not included as a primary focus of the research but was mentioned. European studies reveal that most of the events are related to local symptoms such as pain, swelling, heat and redness. The information following was extracted from a multi-center clinical trial investigation performed in the United States. The injection protocol followed the recommended five time, 2 ml solution injections one week apart. This study contained three levels: Hyalgan treated patients (N = 164); Placebo - control - patients (N = 168); and Naproxen treated patients (N= 163). The mean age across the levels was 64 years with 60% females and 40% males. The adverse events were recorded as: gastrointestinal complaints, injection site pain, headache, local skin reactions (rash, discoloration), local joint pain and swelling and local pruritus (itching). The results were statistically significant in the occurrence of pain at the injection site in the Hylagan patients (23% compared to 13%, p = .022); no statistical significance between the Hyalgan treated group and the control groups concerning gastrointestinal complaints (29% vs 36%), headaches (18% vs 17%), local skin
irritations (14% vs 10%), local joint pain and swelling (13% vs 12%) or pruritus (7% vs 4%). The naproxen treated patients were not mentioned in the results unless they were incorporated into the control group percentages but there was no indication (Sanofi Pharmaceuticals, Inc., 1998).

Simon (1999) found in published literature that several clinical trials testing Synvisc treatment resulted in patients who dropped out of the study due to intense injection site pain. Simon (1999) also noted that subjects treated with Hyalgan left research trials due to injection site pain and in two cases, anaphylaxis was reported following injection. Wright et al. (2000) documented researching the same adverse effects as aforementioned researchers and also noted cases of erythema, muscular cramps, and hemorrhoids linked to viscosupplementation treatment.

Viscosupplementation is a modality that attempts to treat the underlying cause of OA by replacing the HA that affected knees have lost. This means that the watery and unstable joint spaces that plague OA patients, can be restored to cushioned, stable and more “gel-like” environments. Viscosupplementation involves injecting HA directly into the knee joint. Due to the fact that products such as Hyalgan and Synvisc contain forms of hylans, the injected substance is thick and viscous. This “thickness” or higher viscosity may then cause some side effects such as injection site pain and itching. Since both products are actually foreign to the body at initial injection, the body may treat it as such and try to rid it from the body. This could result in adverse reactions such as swelling, pain and heat around the injection site or even within the entire joint. Again, because viscosupplementation is a foreign chemical, certain individuals may react to it in many ways.
different ways creating may different side effects. This, however, happens with all forms of medication. Viscosupplementation has been proven by several studies to be more effective with decreasing joint pain and stiffness and increasing physical functioning than any other treatment for OA. Furthermore, viscosupplementation has also been proven to create significantly less side effects than other popular forms of treatment such as NSAIDS and steroid injections.

**Hyalgan**

Hyalgan is a viscosupplementation modality that is manufactured by Fidia S.p.A. located in Abano Terme, Italy. Hyalgan contains per 2 ml syringe: 20 mg of sodium hyaluronate (extracted from rooster combs); 17 mg of sodium chloride; 0.1 mg of monobasic sodium phosphate 2H2O; dibasic sodium phosphate 12H2O; and up to 2 ml of water. The molecular weight ranges from 500,000 daltons to 750,000 daltons. The recommended administration of Hyalgan is by intra-articular injection, using a 20 gauge needle, 2 ml per injection, once per week for five weeks.

Corrado, Peluso, Gigliotti, De Durante, Palmieri, Savoia, Oriani and Tajana (1995) note that it is widely reported in the literature that intra-articular injections of hyaluronic acid (HA) has beneficial effects in osteoarthritis patients physiologically inside the joint capsule as well as mechanically and symptomatically. Administration of HA can control the secondary inflammatory process and can stimulate the endogenous synthesis of HA intra-articularly. Due to the documented findings, the authors listed above were interested in assessing whether viscosupplementation of HA could, besides controlling pain, induce a
significant change in the WBC (leukocyte) pattern of the synovial fluid in OA patients. They also decided to measure the quantities of proteins that have previously been documented at high concentrations in plasma and synovial fluid. The goal of this research was to assess 2 characteristics: 1). the components of the cell populations present in synovial fluid; and 2). the concentrations of albumin and protein present in synovial fluid. Corrado et al., used 40 patients, 9 males and 31 females with a mean age of 61 years. The diagnosis was mono or bilateral OA of the knee with at least 6 months duration of symptoms. All participants presented at least 3 ml of joint effusions and pain upon movement. The patients were randomly divided into two groups, group A (treated with Hyalgan - sodium hyaluronate) and group B, control group (treated with a placebo). Administration of injections were identical in both groups and consistent with the recommendations already mentioned. Patients were assessed before each injection (days 0, 7, 14, 21 and 28). The main criterion was pain on movement measured by the Visual Analogue Scale (VAS). Secondary criteria was pain at rest also using the VAS, joint mobility on flexion, a five point scale (0 = none, 1 = poor, 2 = fair, 3 = good, 4 = excellent) subjective to physician and patient rating treatment efficacy and the volume of joint effusion aspirated. On day 0 and day 35 tests were completed with blood and synovial fluid analyzing the phenotype characterizations of the WBCs and a quantitative assessment of proteins. Statistical analysis was performed using the ANOVA test for the clinical trials and the Wilcoxon’s test for the invasive variables. The results were (percentages compared to baseline levels which were similar in both groups and following results were recorded at day 35): pain on movement, group A revealed a 50% decrease in
pain and group B a 29% decrease in pain; pain at rest, group A = 78% decrease in pain and group B = 11% decrease in pain; flexion, group A = an increase of flexion by 9.5% and group B showed a decrease in flexion by 4%; for joint effusion there was no statistical significance in either group; physician and patient efficacy rating, positive judgements (good and excellent) were expressed by physician and patient for group A 68% and group B 25%. The results of the in vivo biochemical measurements of the synovial fluid and plasma found reduced levels of WBCs and a general decrease in the various protein species studied. Most of these results were statistically significant ranging from $p = .0006$ to $p = .0482$ and the non statistically significant results ranging from $p = .06$ to 0.7. The results of this study show definite clinical efficacy of sodium hyaluronate in the knee joint. The results also progress toward biochemical efficacy as well. To improve the significance of the biochemical results, the same tests could be utilized comparing an additional level of normal knee joints (Corrado et al., 1995).

Altman and Moskowitz (1998) completed an extensive and extremely detail oriented study that researched the efficacy and safety of sodium hyaluronate (Hyalgan). The study group consisted of 333 participants from 15 different academic and private practice centers. The inclusion criteria included men and women with a mean age of greater or equal to 40 years, a diagnosis of OA of the knee and pain for at least one year, severity of pain (on a 50 foot walk) greater than or equal to 20 mm on a 100 mm visual analog scale (VAS), pain greater than or equal to 20 mm on at least one pain item of the WOMAC subscale, moderate or marked pain on a six point categorical (none, slight, mild, moderate, marked, severe) scale, a knee radiograph of a Kellegren-Lawrence grade two or three, no
prior intra-articular injections of HA within one year, and finally, no other intra-articular injections of any other product for at least three months. The study design was double blind and compared the efficacy of Hyalgan to naproxen and a placebo. All patients received the same treatment protocol no matter which treatment group they were assigned to. Hyalgan patients received the standard intra-articular injection for the respective product and also an oral placebo to simulate naproxen. The naproxen patients received and intra-articular of saline solution and the placebo patients received saline solution injection and an oral placebo cosmetically identical to naproxen. All patients were blind to what they were receiving and were even draped while receiving the injection. There were two researchers, one masked and the other unmasked. The blinded researcher performed and recorded efficacy assessments and was not present for injections or privileged to any study data. The non-blinded researcher recorded adverse events, monitored laboratory reports, assured patient blindness, and performed the injections. Participants were allowed to take 500 mg acetaminophen tablets up to 4000 mg/day as needed for knee pain and were monitored with subject recorded intake and laboratory results. Treatment efficacy was assessed by pain during a 50 foot walk, measurement of knee pain during previous 48 hours by a six point scale, time in seconds to complete a 50 foot walk, WOMAC index by VAS, heel to buttocks distance in cm, knee range of motion measured in degrees by goniometer, midpatellar knee circumference in mm, clinical estimate of synovial effusion of the knee, acetaminophen count, and overall evaluation of treatment effectiveness by the patient and masked observer. For efficacy, Hyalgan resulted in a significant improvement with all assessments compared to the naproxen and placebo groups. The naproxen group

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exhibited a lower subject usage of acetaminophen than the Hyalgan or placebo group. For safety, there were significantly more gastrointestinal adverse events associated with naproxen than with Hyalgan or placebo subjects. Complaints of injection site pain were significantly higher in the Hyalgan group. Ecchymosis, rash, headaches, and pruritus revealed no statistical difference among any group and were noted in all. There were four reports of severe knee swelling and/or effusion, one in each naproxen and placebo group and two in the Hyalgan group. The efficacy and safety measurements of this study ultimately support that Hyalgan when compared to naproxen or a placebo is the preferred method of treatment for OA of the knee with significant pain reduction, functional improvement and no major adverse effects when compared with the other two study groups (Altman & Moskowitz, 1998).

There is another type of viscosupplementation product which is also characterized by a molecular weight ranging between 500,00 daltons and 750,000 daltons and containing mostly sodium hyaluronate. This product, ARTZ (Seikagaku Co.), is currently being used in the Asian countries but not in the U.S. Wu, Shih Hsu, and Chen (1997), also compared sodium hyaluronate (ARTZ) with a placebo. Participants consisted of 90 patients with 116 knees diagnosed as mild to moderate osteoarthritis. The diagnostic criteria included symptoms with exercise pain, decreased ROM, radiologic findings of bone spurs, joint space narrowing or osteosclerosis. The research design was double-blinded using two groups. The test drug was 2.5 ml of a sodium hyaluronate solution and the placebo was 2.5 ml of a solvent for ARTZ. The injection protocol for both groups used the five injection administration once a week for five weeks. No local anesthetics,
NSAIDs or physical therapy were allowed. Evaluation items were clinical symptoms and were as follows: resting pain, walking pain, up/down stairs pain, flexion/extension pain, oppressive pain, swelling, estimated amounts of synovial effusion, and ROM of joints. The parameters were subjective and divided into four categories: no symptoms, mild, moderate or severe symptoms. The synovial fluid was measured in milliliters (ml). Other evaluations included general improvement and was judged by evaluating clinical symptoms and daily activities comparing before and after treatment values. These values were ranked in seven categories: 7 excellent improvement, 6 improved, 5 fair improvement, 4 unchanged, 3 slightly worsened, 2 worsened, and 1 markedly worse. All parameters were recorded at zero weeks and five weeks, before each injection and one week after total injections. Statistical analysis was calculated using the ANOVA, Student's t-test, Mann-Whitney U test and Chi-Square. Results indicate that there was a statistically significant improvement in all areas of the ARTZ treated group compared to the placebo group and both compared to baseline measurements. The most prominent improvement was the efficacy of ARTZ for relief of motion pain and increased ROM. Also, the largest margin of difference and most improvement across the board was found between five weeks and 13 weeks. After 13 weeks, the margin narrowed and the treatment effects decreased. This results in marked efficacy between three and six months. During this research, there were no patient complaints of side effects and no adverse events recorded.

Wobig, Bach, Beks, Dickhut, Runzheimer, Schwieger, Vetter and Balazs (1999) published a study that compared hylan GF-20 (Synvisc - 6 million daltons) to a lower molecular weight hyaluronan (ARTZ - 0.75 million daltons). The purpose of their study
was to compare the viscoelastic properties of Synvisc and ARTZ to determine a relationship of elastoviscosity to positive treatment outcome in patients with osteoarthritis of the knee. The study was a 12 week, double blinded, randomized, multi-center study with a total of 70 patients (38 received Synvisc and 32 received ARTZ). The patient inclusion criteria required a radiographically confirmed diagnosis of primary idiopathic OA of the knee, a certain amount of erythrocyte sedimentation, and knee pain that was unaffected by other treatments. Treatment initiation followed a two week washout period and was exactly the same for each product. The participants were randomly separated into the two groups, either Synvisc or ARTZ, and were given 2 ml injections of the respective solutions to knees with no effusion using 18 to 20 gauge needles. In both groups, there were three injections given at one week intervals between each injection. Efficacy determination was based on results from the WOMAC index and adverse reaction results were based on patient interviews. The statistical analysis resulted in Synvisc having a significantly greater pain relieving effect than ARTZ with no significantly greater incidence of adverse effects.

Mensitieri, Ambrosio, Iannace and Nicolais (1995) compared the efficacy of two knee osteoarthritis therapies: viscosupplementation with sodium hyaluronate and arthrocentesis (aspiration of knee effusion). This study deals with the rheological evaluation of synovial fluid. Fluids were extracted before and after viscosupplementation, arthrocentesis and placebo therapies to obtain and measure entities that could explain the efficacies of each. The synovial fluid was extracted from 60 patients who had clinical and radiological signs of OA for at least six months. The participants were randomly assigned to three different
groups: the exogenous HA group, the placebo group and the arthrocentesis group. The HA group was injected with Hyalgan according to the recommended five injection, one week margin, guidelines. The placebo group was also injected according to the same guidelines as the HA group but with 2 ml of placebo. The rheological properties of the extracted synovial fluid was measured using a Bohlin VOR Rheometer. The viscoelastic evaluation of the efficacy of the different therapies was based on the analysis of synovial fluid frequency sweeps which indicated that the fluid in all groups before treatment was diluted resulting in a reduction of rheological properties. The same measurement was utilized in the synovial fluid extracted after the treatment and this is what Mensitieri et al. found. The arthrocentesis yielded synovial fluid with a decrease in HA concentration and molecular weight and an increase in concentration of proteins. There is no endogenous stimulation of HA in the joint capsule following arthrocentesis. The Hyalgan treated group showed an increase in HA concentration and molecular weight. The authors of this study state that the hypothesis that exogenous HA enhances the in vitro production of HA can be confirmed by this rheological analysis (Mensitieri et al., 1995). The conclusion is that even though viscosupplemented HA has been proven by other research to be short lived in the joint capsule, that short time can stimulate the production of endogenous HA. This is an important finding considering that OA is a degenerative disease that has received only treatment for the symptoms. Perhaps the longer a patient receives HA injections, the more endogenous HA can be stimulated from its own tissues.

The focus of a study completed by Kotz and Kolarz (1999) consisted of three objectives for patients treated with Hyalgan. The first objective was to research time
intervals from the first sign of improvement following the initial injection. The second objective was the duration of improvement after the treatment cycle (all 5 injections) and lastly following a second treatment cycle if a renewed need for therapy occurred the fourth month and twelve month after the fifth injection from the first cycle. Subjects consisted of 77 women with a mean age of 59.5 years and 31 men with a mean age of 53.0 years. Participant criteria included sole diagnosis of OA of the knee, subjective complaints for one year, knee pain for at least 20 days of the month, and a value of greater than or equal to 3.3 on a 10 cm visual analog scale (VAS) with 0= no pain and 10=maximum pain concerning numerous activities. The last criteria would serve as baseline measures and would be taken before beginning any treatment. Examinations were performed at day 0, 7, 14, 21, 28, and 35 during the treatment cycle and then monthly thereafter. Treatment safety was assessed by monitoring several various laboratory tests and by recording any adverse effects that may have occurred between each exam. If there was a need for any subject to begin another cycle of treatment the first injection of the second cycle could begin anywhere between the end of the fourth month and the beginning of the twelfth month. Patients engaging in a second cycle were monitored the same as the first cycle. This study resulted in three years of research from 1991 to 1994. Statistical analysis was performed by using Student’s t test, with the alpha level set at p<0.05. The study resulted in an improvement in 95% of the subjects with descriptions ranging from symptom free to slight improvement. There were 119 instances of adverse effects recorded ranging from back pain, injection site reaction, injection site pain, and joint effusion (Kotz & Kolarz, 1999).
Many other studies have been completed focusing directly on Hyalgan but the research was performed “in-house” and is unavailable in published literature. The following information was supplied directly from the company which markets Hyalgan. A double blind, three level (Hyalgan, naproxen, and control), 26 week study used 495 patients ranging in age between 40 and 90 years to test the efficacy of Hyalgan (sodium hyaluronate). Clinical assessments included the Visual Analog Scale (VAS) and the Western Ontario and McMaster University Osteoarthritic Index (WOMAC). Hyalgan patients received the recommended administration of Hyalgan as mentioned earlier and a naproxen placebo. Naproxen patients received 500 mg b.i.d. (twice per day) and no injections and the control patients received a naproxen placebo plus saline injections following the same protocol as the Hyalgan group. All patients received subcutaneous lidocaine and were allowed to take no more than 4 g/day of acetaminophen. The results showed that the Hyalgan patients achieved a statistical significance in the VAS 50 foot walk category and maintained the improvement for over six months (p=.03 compared to the control group and comparable to naproxen). In the patient’s categorical assessment of pain the percentages of slight or no pain were as follows: Hyalgan 47.6%; Naproxen 38.9%; and control 33.1%. Injection site pain was the only adverse event occurring more in the Hyalgan group (23%) than the control group (13%). Other adverse events such as headaches, GI irritation, itching, etc. were not significant to any group.

Research studies have found that Hyalgan significantly decreases pain and stiffness and increases range of motion and daily functioning. Studies have also concluded that the use of Hyalgan through viscosupplementation may actually stimulate the body to begin...
manufacturing small amounts of endogenous HA. Although there were a number of adverse events linked to the utilization of Hyalgan, the research strongly suggests that there are still less side effects resulting from Hyalgan injections than other forms of treatment (NSAIDS, etc.) and more importantly, Hyalgan’s treatment was much more effective than those other forms of treatment.

**Synvisc**

Synvisc is a viscosupplementation modality that is manufactured by Biomatrix located in Ridgefield, New Jersey. Synvisc contains per 2 ml syringe: 16 mg Hylan A and B; 17 mg sodium chloride; .32 mg disodium hydrogen phosphate; .08mg sodium dihydrogen phosphate monohydrate, and water. The molecular weight ranges from 4 million daltons to 6 million daltons. Recommended injection of Synvisc is intra-articular injection. 2 ml syringe with an 18 gauge needle, once a week for three weeks.

Adams, Atkinson, Lussier, Schulz, Siminovitch, Wade and Zummer (1995) conducted a study to determine the safety and efficacy of viscosupplementation with hylan GF-20 (Synvisc) used either alone or along with continuous NSAID therapy. The purpose was to evaluate whether hylan GF-20 can prevent a flare in pain when NSAID therapy is discontinued. The 93 patients were men or women between the ages of 18 and 75 years with a diagnosis of idiopathic OA of the knee. Patients had to satisfy some of the following criteria: 1) morning stiffness not longer than 30 minutes; 2) crepitus on active motion; 3) tenderness of the bony margins; and 4) physician determination of absence of rheumatoid disease. All the participants also needed to have been taking NSAID therapy.
for at least 30 days prior to trial without significant side effects, to have been actively using the affected joint on a daily basis and a VAS score of >50 mm out of 100 mm for pain on motion with weight bearing. Patients were then randomly assigned to one of three treatment groups. The NSAID only treatment group received a series of three weekly arthrocenteses and continued to take the NSAIDs as before and throughout the trial. The Hylan GF-20 only group discontinued the NSAID dosage and instead only received viscosupplementation according to the recommended guidelines, 2.0 ml per week for three weeks. The third group continued the before trial NSAID dosage in addition to receiving injections of hylan GF-20 following the group two protocol. No placebo group was included. No other treatment was allowed except acetaminophen which was only to be taken upon emergency basis. If acetaminophen was ingested, the participant was to document reasons and dosage in a daily diary and was instructed to notify the investigators. Patients were evaluated before injections began for baseline values. The subsequent evaluations were at each injection three weeks apart, at week 7 and week 12. The patients were also evaluated through a phone interview at week 26. Efficacy variables were measured at each meeting using a 100 mm VAS. The variables were: pain on motion with weight bearing; pain at rest; pain at night; restriction of activity; patient’s overall assessment of arthritic pain; pain during a 50 foot walk; medial joint tenderness; and evaluator’s overall assessment of the treatment. Efficacy variables were measured on an ordinal scale correlating numbers with signs and/or symptoms. Adverse events were also reported and recorded at each visit. Categorical analyses were performed for each outcome measure defining improvement at a VAS score of below 20 mm. ANOVA was
used for analysis of continuous data and comparisons among the three groups. Fisher's LSD multiple comparisons test was used to distinguish between individual treatments. Paired t-tests were used to evaluate efficacy by comparing pre and post treatment values. The chi-squared test and tests of proportions were used to analyze categorical data. For the severity of pain variable which did not follow continuous distribution, an ANOVA of ranked data was used. Least square means were calculated from the individual improvements and used for comparisons among all three groups (Adams et al., 1995). The only statistically significant results up to the 12 week evaluation among the groups were found for pain at night and support used. Although both groups of hylan injected patients showed better results than the NSAID alone treated group, the results were not statistically different. This explains that hylan GF-20 is at least as effective as NSAIDs up to 12 weeks. At the 26 week phone interview, the data obtained did demonstrate some statistically significant differences. Data was received from the patient by only using the patient-evaluated VAS variables as in all the previous evaluations. The investigator was only able to judge the patient's perception of the clinical condition rather than actually performing it. The hylan groups both showed significantly less pain at this time then the NSAID only group. This could mean that there are benefits occurring up to six months following one course of hylan injection. Adverse events were reported and recorded. Only 6 patients of the 93 were documented as having some type of adverse event during the trial. Three of those participants were excused from this category because the events were not related to the injection but instead unrelated factors. The three participants who remained in this category all began to experience the adversity approximately 24 hours
following injection including warmth effusion and a high WBC count in their synovial fluid. These side effects were recorded as not severe and were absent with in a week. Although this study was extensive and lengthy, what needs to be deduced is that the results show that hylan GF-20 is at least as effective as NSAIDs in the relief of pain and increase in activity and maybe even more so, just not supported statistically. There was a minimal number of side effects reported and the efficacy seems to be lengthy.

Lussier, Cividino, McFarlane, Olszynski, Potashner, and Medicis conducted a long term, case study style investigation of hylan GF-20 on 336 patients (458 knees) from 1992 to 1995. The information collected from each patient included demographics, disease characteristics, injection technique, and information with respect to hylan treatment history such as efficacy and adverse reactions. Participants consisted of 125 males and 211 females with a mean age of 65 years. Patients underwent two courses of viscosupplementation. Each course consisted of three, 2 ml injections of hylan GF-20 once a week for three weeks. Clinical efficacy was evaluated by the patient's opinion of treatment and any changes in pain or activity level. This was measured on a five factor ordinal scale (much better, better, same, worse, much worse). Following the first course, 77% of the knees were either better or much better with pain and following the second course, 87% of the knees fell under the same two categories. Activity level after the first course was 76% better to much better and following the second course, 84% were better to much better. The survey also collected data on any changes in the patients normal use of pain relief therapy after the viscosupplementation treatment. Over half of the participants either decreased or stop using any additional form of therapy such as
analgesics, NSAIDs or steroidal medication. Radiological data was gathered from these patients to compare the in vitro response to hylan injections. Grades I, II and III OA were studied and although there was improvement seen in all cases, only a statistically significant difference (using chi-square analysis) was noted in the early and intermediate stage patients compared to the end stage of OA (p = .05). The duration of clinical benefit after hylan injection was analyzed in two ways. The first method was based on the evaluation of the investigator which led to the opinion that the majority of patients demonstrate clinical benefits from three months to 12 months. The second method was based on the time that elapsed between the first course of treatment and the patient’s need for a second course of treatment. The mean duration was eight months with a range of two to 18 months. Twenty eight patients reported local adverse events mainly pain, swelling and heat and on a mild to moderate level. 72% of the reactions were considered to be possibly or probably due to the hylan injection. These adverse events were transient in most patients with no further problems. The relationship between the incidence of adverse events and the injection technique used to administer the hylan were documented. The categories for injection entry were: medial straight; medial flexed; lateral straight; lateral flexed; and intrapatellar. The greatest percentage of adverse events was observed with a medial flexed approach which was statistically significant to the other categories (p=.014 - p=.017) (Lussier et al.). Conclusions of this study are that hylan GF - 20 seems to be effective in the decrease of OA symptoms and can last several months with a low incidence of adverse effects.
As with Hyalgan, research studies have found that Synvisc is significantly more effective in decreasing pain and stiffness and increasing range of motion and daily functioning than other forms of treatment such as NSAIDS, analgesics, saline, etc...

Furthermore, Synvisc is more easily tolerated than other forms of treatment and although adverse reactions have been noted, they are significantly less than associated with the utilization of other forms of treatment.

Hyalgan vs Synvisc

In 1997, the FDA approved the only two products to be used as viscosupplementation therapeutic devices for osteoarthritis of the knee in the United States. Hyalgan and Synvisc. The previous documented review of literature provided numerous facts revealing the differences in these two products in consistency, molecular weight, and incidence of adverse reactions. In addition to product efficacies, another consideration of high importance to the patient is economics. As mentioned earlier, NSAIDs have an average cost of roughly $55 per month. The actual wholesale price (AWP) for Hyalgan is approximately $635 per course of therapy (5 injections). Synvisc's AWP is approximately $619 per course of therapy (3 injections). Ultimately, the cost for the patient, depending on insurance, will equal about 20% of a price equal to the AWP or lower. For example, the price for Hyalgan users will be approximately $120.60 per course of therapy and the price for Synvisc will be about $117.74 per course of therapy. Over a 4-6 month course of treatment, the cost per month ranges between $20 and $30 per month, a definite economic value over continued NSAID use. The research also revealed the efficacy of
both products in treating OA of the knee and the superiority of viscosupplementation treatment as compared to NSAIDS or placebo treatment groups. To date, there have been several studies comparing each product to other forms of OA treatment or efficacy against some type of control or placebo group but no published information has been found directly comparing the efficacy or functional outcomes of each product to the other.

Research supports that, in most cases, viscosupplementation is the most effective choice in the treatment of osteoarthritis of the knee as it attempts to treat the underlying cause of the disease rather than the associated symptoms. Currently, doctors and patients in the U.S. have two FDA approved product choices. Hyalgan and Synvisc. Although Hyalgan and Synvisc have identical overall goals, there are also many significant differences between the two viscosupplementation products. The two most prominent differences surround the molecular weight and injection protocol, both of which have been linked to the incidence of adverse reactions. Based on the differences between these two products as identified in the literature, this research study will directly compare Hyalgan to Synvisc in an attempt to determine if there are any overall efficacy or adverse event differences between the two viscosupplements.
CHAPTER 3

METHODS

Participants

Forty - one participants (20 Hyalgan, 21 Synvisc) mixed in gender, age, and ethnic background volunteered through their physician's office to participate in this study.

Twelve men and eight women with a mean age of 64 years comprised the Hyalgan group and 15 men and six women with a mean age of 62 constituted the Synvisc group. The physicians were utilizing viscosupplementation prior to becoming study contributors. Volunteers for this study were patients of these physicians who already made the decision to try viscosupplementation as a treatment. A clinical diagnosis of osteoarthritis of the knee must have been made by the treating physician prior to the study. Participants were excluded if they had any previous experience with viscosupplementation treatment, engaged in any form of physical rehabilitation or exercise therapy for OA of the treatment knee, planned to initiate any prescription analgesic or anti-inflammatory medication after the first injection, consumed glucosamine supplements, received saline lavage, or corticosteroidal injections. The patients using over the counter analgesics and anti-inflammatories on a regular basis and at a consistent dosage to treat their OA prior to the
first injection were allowed to continue using the medication but were not allowed to
increase the dosage or frequency. This study was approved by the University of Nevada,
Las Vegas Institutional Review Board (Appendix A) and all participants signed informed
consent forms prior to participation (Appendix B). Participants were informed of their
right to withdraw from the study at any time.

Instrumentation

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
(Appendix C) was developed by Dr. Nicholas Bellamy in 1981. The WOMAC is a tri-
dimensional, disease specific, self administered, health status measure (Bellamy, Buchanan,
Goldsmith, Campbell, & Stitt, 1988) that is utilized for the detection of clinically
important changes in health status of osteoarthritis following a variety of interventions
such as: non-steroidal anti-inflammatories (NSAIDS), analgesics, physical therapy,
corticosteroids, joint replacement, arthroplasty, and viscosupplementation (Bellamy &
Buchanan, 1986; Bellamy, Wells, & Campbell, 1991; Bellamy, Buchanan, & Chalmers.
1992). The WOMAC is an index consisting of 24 questions that focus on clinically
important symptoms in patients with osteoarthritis of the hip and/or knee. The questions
include: five pain, two stiffness, and 17 physical function (daily activities), and can be
completed in less than five minutes. Bellamy, Buchanan, Goldsmith, Campbell and Stitt
have completed two major studies to assess the validity and reliability of the WOMAC
index. Both studies concurrently administered the WOMAC index along with the
Modified Doyle Index, the Lesquesne Index, the Bradburn Index of Well-Being, and the
Social Component of the MHIQ to the participants for validation purposes. Reliability
was tested with pain, stiffness, and daily function and determined using Cronbach's alpha. Values for pain were: pre = 0.88, mid = 0.88, and post = 0.93. Values for stiffness were: pre = 0.87, mid = 0.73, and post = 0.96. Values for daily function were: pre = 0.88, mid = 0.91, and post = 0.94. Test-retest reliability was determined using Kendall's tau c statistic and by using a one week retest interval the values were: pain = 0.64, stiffness = 0.61, and daily function = 0.72. This study utilized the visual analog (VA) scaled version of the WOMAC which requires the subject to respond on a 10 cm horizontal line with end markers that represent extremes. The left end marker describes no pain, stiffness or difficulty in function for the subject and the right end marker describes extreme pain, stiffness or difficulty in function for the subject. The subjects placed a mark, preferably an "X", on the line where it best represents the way they were feeling at that time in relation to the question.

Viscosupplements

Hyalgan is a viscosupplementation product that is manufactured by Fidia S.p.A. and distributed in the United States by Sanofi Pharmaceuticals, Inc. A 2 ml syringe of Hyalgan contains: 20 mg of sodium hyaluronate, 17 mg of sodium chloride, 0.1 mg of monobasic sodium phosphate 2H₂O, dibasic sodium phosphate 12H₂O, and up to 2 ml of water. The molecular weight of Hyalgan ranges from 500,000 daltons to 750,000 daltons. The recommended administration of this product is through intra-articular injection, using a 20 gauge needle, 2 ml per injection, once per week for five weeks.
Synvisc is a viscosupplementation product manufactured by Biomatrix. Synvisc contains per 2 ml syringe: 16 mg of Hylan A and B, 17 mg sodium chloride, 0.32 mg disodium hydrogen phosphate, 0.8 mg sodium dihydrogen phosphate monohydrate, and water. The molecular weight ranges from four million daltons to six million daltons. Recommended administration of Synvisc is a 2 ml intra-articular injection with an 18 gauge needle, once a week for three weeks.

Procedures

Subjects were patients who were previously identified by their participating physician as candidates for a viscosupplementation program for the treatment of osteoarthritis of the knee. To participate in this study, the subjects read an information packet which explained in detail what was expected of them and then signed a consent form (Appendix B). Subjects were permitted to continue any medication that they were previously taking prior to initiating the program including over the counter NSAIDS and analgesics, and were asked to engage in no form of physical therapy or prescribed exercise. Once the patients agreed to participate in the study, the WOMAC was introduced and completed as a pre-test measure before receiving the first injection of either Synvisc or Hyalgan.

Forty one patients (20 Hyalgan, 21 Synvisc) received either Hyalgan or Synvisc throughout the research protocol and were not permitted to switch or combine products. The products were administered identically by the participating physicians. Since the incidence of adverse events related to the injection site are significantly influenced by the injection technique, we chose a lateral entry with a straight knee (Lussier, Cividino, 

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McFarlane, Olszynski, Potashner, & De Medicis, 1996) using a 20 gauge needle. Hyalgan patients received one injection per week for five weeks and Synvisc patients received one injection per week for three weeks. Two months following the completion of injections, each subject received, by mail, a WOMAC questionnaire that served as the mid-test measure. Participants received the final WOMAC, four months after the final injection which served as the post-test measure. With the exception of the time required to complete the WOMAC, subjects did not incur any additional expenses due to their participation in this study as they were going to receive viscosupplementation treatment regardless of their participation in the study.

Upon completion of the three WOMAC questionnaires, the researchers used a ruler to determine the distance in millimeters from the left end marker of each line to the point at which the patients mark intersected the line on the analogue scale. For each section (pain, stiffness, daily activity) a sub-scale score was calculated by the summation of each measurement. For example, the total range for scores for pain was 0-500, for stiffness 0-200, and for daily function 0-1700.

Data Analysis

Mean scores were analyzed using a 2 (Treatment) x 3(Time) factorial analysis of variance (ANOVA) with repeated measures on the second factor (Time). Separate ANOVA's were used for each dependent variable: pain, stiffness, and daily function to determine if there was a significant difference in functional efficacy between Hyalgan and
Synvisc at pre-injection, two month post-injection, and four month post-injection and to also determine overall product efficacy (please see Appendix D for raw data).
CHAPTER 4

RESULTS

Pain

Research participants responded to five questions from each WOMAC questionnaire (15 total: pre-test, two month test, and four month test) regarding the intensity of their knee joint pain during various levels of activity. With each questionnaire, there was a total possible score for pain ranging from 0 to 500 for both Synvisc and Hyalgan. A significant pre-test difference was found between Hyalgan and Synvisc participants prior to the first injection for either group. Synvisc patients described a significantly higher initial pain intensity (M=311.57) than Hyalgan patients (M=229.20) (p<0.05) possibly due to a number of high outlier scores or low outlier scores (see Appendix E for scatterplot scores). However, the two month WOMAC results revealed no significant difference regarding pain between Synvisc patients (M=197.95) and Hyalgan patients (M=177.20) (p>0.05). Similarly, the four month WOMAC results also yielded no significant differences between Synvisc (M=117.95) and Hyalgan (M=97.15) (p>0.05). Furthermore, there was a significant interaction between pain scores and time (p<.01) possibly due to the fact that there was a significant difference between the pain scores of...
the Hyalgan and Synvisc groups on the initial WOMAC testing prior to the commencement of the viscosupplementation protocol.

![Graph](image)

Figure 1. Effects of Viscosupplementation on pain over time.

**Stiffness**

The WOMAC consists of two questions pertaining to knee joint stiffness. The participants answered the two identical questions on each WOMAC administration, equaling six stiffness questions in all. The total possible score for stiffness on each questionnaire could range from 0 to 200 for both Hyalgan and Synvisc participants. Again, the pre-test results revealed that there was a significant difference between Synvisc patients and Hyalgan patients concerning perceived degree of stiffness prior to any injection of either product. Synvisc patients complained of significantly worse stiffness (M=134.00) than did Hyalgan patients (M=102.30) (p<0.05) again, possibly due to a number of initial outlier scores for Synvisc (see Appendix E for scatterplot scores). Similar to the pain results, by the two month questionnaire Hyalgan patients conveyed no
significant differences concerning stiffness ($M=72.60$) compared to Synvisc patients ($M=90.86$) ($p>0.05$). Again, the same was true for the four month WOMAC, as the differences between Synvisc ($M=58.19$) and Hyalgan ($M=43.20$) were not significant ($p>0.05$).

![Stiffness Graph](image)

Figure 2. Effects of viscosupplementation on stiffness over time.

**Daily Activities**

Questions regarding daily activity (functioning) comprise the major construct of the WOMAC questionnaire. There were 17 questions to answer for each WOMAC administration in regard to daily functioning, with individual scores ranging from 0 to 1700 for each patient (see Appendix E for scatterplot scores). The results suggest that there are no significant differences for daily functioning between Synvisc patients (pre-test $M=1066.5$; two month test $M=640.6$; four month test $M=361.95$) and Hyalgan patients.
(pre-test M=890.4; two month test M=597.3; four month test M=340.45) within each of the three WOMAC administrations.

**Daily Activities**

![Graph of Daily Activities Over Time](image)

Figure 3. Effects of viscosupplementation on daily activities over time.

**Overall Effectiveness**

Although the purpose of this research was to compare and not question the effectiveness of Hyalgan and Synvisc in their improvement of OA symptoms, this study, as well as several preceding publications, resulted in finding that both products are highly effective in decreasing pain and stiffness and increasing daily functioning. For Hyalgan the results concluded that there was a significant difference in the decrease of pain from pre-test through the four month test (p<.0001). There was also a significant decrease in stiffness (p<.0001) and a significant increase in daily functioning (p<.0001). The same was also true for Synvisc resulting in a significant decrease in pain from pre-test through...
the four month test ($p<.0001$), a significant decrease in stiffness ($p<.0001$), and a significant increase in daily functioning ($p<.0001$) among the participants.
CHAPTER 5

DISCUSSION

The efficacy of viscosupplementation products for OA of the knee have been researched extensively especially in comparison to other forms of treatment for osteoarthritis. Published results for these products support that they are highly effective in decreasing pain and stiffness and increasing daily functioning for patients with OA. Equally as important, studies have proven that viscosupplementation also yields by far the smallest incidence of adverse effects when compared with other means of OA treatment such as NSAIDS, analgesics, glucosamine, saline lavage, steroids, physical therapy, and knee replacement (Creamer & Hochberg, 1997; Dieppe et al., 1993; Harris, 1993; Wen, 2000; Goorman et al., 2000; Wright et al., 2000; Uebelhart & Williams, 1999). As a result of these findings, viscosupplementation is becoming an increasingly popular and preferred treatment every year. Currently, the two FDA approved viscosupplementation products, Hyalgan and Synvisc, are supported by vast publications concerning their effectiveness in treating OA symptoms against the other types of treatments.

The relationship between the molecular weight and viscosity of each the treatment products and functional efficacy has been a top priority of the research to determine whether or not viscosity is a key reason for the positive effectiveness. Most published
studies such as one completed in 1994 by Aviad and Houpt, suggest that there are no significant differences in product efficacy when comparing molecular weight. However, a more recent study by Wobig et al. (1999) comparing Synvisc (6 millions daltons) to ARTZ (similar to Hyalgan at 0.75 million daltons) concluded that Synvisc was significantly more effective than ARTZ in decreasing pain and stiffness and increasing function. The authors credited these findings to the much higher molecular weight of Synvisc, explaining that a higher molecular weight product is more beneficial than a lower molecular weight product. The importance of this study to our research revolves around the similarities between Hyalgan and ARTZ in both composition and molecular weight. Physician and/or patient knowledge of these similarities could infer that if Synvisc is more efficacious than ARTZ then the same must be true for Hyalgan. The results from this study suggest that there are no significant differences between Hyalgan and Synvisc when comparing treatment efficacies, protocol, incidence of adverse reactions, or cost to patient.

The study performed by Wobig et al. (1999) utilized 70 participants total based on a comparison of treatment groups using a two-tailed t test with an alpha factor of 0.05 and a power of 0.8, meaning the minimum required sample size was 29 participants for each group, a grand total of 58 patients. Our research utilized 20 Hyalgan and 21 Synvisc patients, 41 participants total. Both the Hyalgan versus Synvisc study and the Synvisc versus ARTZ study required very similar inclusion criteria for participants, used a marginal number of participants, used a multi-center approach, relied on the WOMAC guide for data and used similar statistical analysis to produce the results. The key difference between the Synvisc/ARTZ and the Synvisc/Hyalgan studies was the injection protocol.
Our study specifically followed the injection protocols recommended by each company. Synvisc, due to its higher molecular weight, is to be administered in a course of 3 injections while the lower molecular weight Hyalgan requires five injections. Wobig et al. administered three injections of ARTZ which resulted in approximately 1 million 5 hundred thousand daltons less than what the recommended protocol of five injections provides. Therefore when comparing overall treatment protocols, the ARTZ participants were not receiving as much overall fluid viscosity (i.e. treatment) as the Synvisc participants. As our study followed the suggested three Synvisc or five Hyalgan injection protocols, the overall molecular weight of the viscosupplement injections was relatively similar across the two viscosupplements and may have eliminated any significant differences between the two products. As such, it may be the overall amount or weight of the viscosupplement that is injected throughout the course of the protocol that is crucial in overall functional efficacy rather than the importance of the molecular weight of each individual viscosupplement.

Other studies focusing on the molecular weight of viscosupplementation products are concerned with a possible increase in the incidence of adverse effects due to higher molecular weight compounds. Several researchers such as Puttnick et. al (1995) claim to have found more adverse reactions such as increased injection site pain and swelling in products with a higher molecular weight than with lower or very little molecular weighted substances. Other studies indicate an increased participant drop out rate associated with extreme injection site pain after the use of a high molecular weight substance. There are also reports of injection site problems with lower molecular weight substances but not as
extreme or as extensive. However, all of these studies compared the viscosupplementation product with saline injections, a placebo effect, or no injection at all. The study by Wobig et al. (1999) that compared two viscosupplementation products, did not mention any major problems with the injection site. The results of our study suggested no differences between the higher molecular weight treatment and the lower molecular weight treatment regarding any type of injection site problem. However, the WOMAC guide is not equipped with questions to indicate if the patient is having any trouble with the injection site and these types of problems are generally either verbally reported to the treating physician or by the participant halting further viscosupplementation treatment.

Our study suggests that Hyalgon and Synvisc are both effective in their ultimate ability to decrease pain and stiffness and increase daily functioning. The purpose of this study, however, was not to determine the overall efficacy of either Hyalgon or Synvisc in the treatment of OA of the knee, but to compare the two. As previously mentioned, the findings of this research did suggest that both viscosupplementation products produced a significant decrease in pain and stiffness, and an increase in the daily function for patients plagued with OA of the knee. However, there was a significant difference between the products at the pre-test level. Before any type of treatment was administered, either Synvisc patients recorded a significantly higher incidence of pain and stiffness or the reverse, Hyalgon patients recorded a significantly lower incidence of pain and stiffness. It is important to mention again that these groups were randomly selected for each treatment group and that these significant differences were recorded prior to any form of treatment.
This was the pre-test WOMAC questionnaire. Reasons for this significant difference between Hyalgan and Synvisc subjects at pre-test are unclear and could be explained by many different scenarios. Coincidence could be one explanation in that there could have been a few outliers whether high or low that just happened to be experiencing more or less pain and stiffness than the rest of the subjects. Perhaps weather played a role in the high outlier perspective whereas a few subjects located in the same area experienced more pain and stiffness due to colder weather conditions at the time of the pre-test. Some subjects may have been confused while filling out the WOMAC for the first time during pre-test. Perhaps directions for completion of the WOMAC differed from patient to patient and seemed unclear by some. Gender may have played a role or possibly just individual pain tolerance. In any event, and there could be many more possibilities, the important issue is the ultimate effectiveness for these patients once they did begin treatment. Once the two month (mid-test) WOMAC was completed, there was no significant difference between Hyalgan and Synvisc for their efficacy in decreasing pain and stiffness and increasing daily functioning. The same was true upon completion of the four month (post-test) WOMAC. Hyalgan and Synvisc were not significantly different with patient improvement of OA symptoms. Because of these findings that Hyalgan and Synvisc are comparably effective in the treatment of OA of the knee, the results will aid in decision making for physicians and patients between Hyalgan and Synvisc depending on individual preferences concerning product, injection protocol, product availability and possibilities of adverse reactions.
Directions for Future Research

Future study is needed to compare all types of viscosupplementation products approved for use. Research of such nature needs to be conducted to determine and confirm the proper treatment protocol suggested by each product company. The differences in fluid content regarding the amount of HA or molecular weight, require specific injection guidelines for each product. Due to the mention in several published studies of localized and more serious adverse reactions, a larger participant group, possibly N=100, for each approved viscosupplementation product would be highly recommended. In addition, due to findings of this study, it may be beneficial to analyze pre-test results before administering treatment to assure that study group recordings are accurate. The cost of treatment deters some patients from either participating in a viscosupplementation program or unwilling to expend the extra effort that would be required as a study participant. Therefore, compensation for the cost of the treatment for anyone willing to participate is highly advisable and would open the door to the use of additional measuring tools and could increase the sample size for each treatment group.
REFERENCES


Sanofi Pharmaceuticals, Inc... (March 1998). Unpublished In-House Data. Data on file with Sanofi Pharmaceuticals, Inc. NY, NY 10016


APPENDIX A

IRB APPROVAL
DATE: November 5, 1998

TO: Colleen Hall-Patton (SOC-5033)

FROM: Dr. William E. Schulze, Director
Office of Sponsored Programs (X1357)

RE: Status of Human Subject Protocol Entitled:
"Hyalgan Versus Synvisc: A Comparison of the Functional Efficacy of Osteoarthritic Knee Joints Following Visco-supplementation Treatment"

The protocol for the project referenced above has been reviewed by the Office of Sponsored Programs and it has been determined that it meets the criteria for exemption from full review by the UNLV human subjects Institutional Review Board. This protocol is approved for a period of one year from the date of this notification and work on the project may proceed.

Should the use of human subjects described in this protocol continue beyond a year from the date of this notification, it will be necessary to request an extension.

If you have any questions regarding this information, please contact Marsha Green in the Office of Sponsored Programs at 895-1357.

cc: S. Pero (KIN-3034)
OSP File

OFFICE OF SPONSORED PROGRAMS
4505 Maryland Parkway • Las Vegas, Nevada 89154-4013
Phone 702-895-1357 • Fax 702-896-4242

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DATE: October 20, 1999

TO: Stephanie Beaseley

3334

FROM: Dr. William E. Smulze, Director
Office of Sponsored Programs (X1357)

RE: Status of Human Subject Protocol Entitled:
"Hyalgan Versus Synvisc: A Comparison of the
Functional Efficacy of Osteoarthritic Knee Joints
Following Visco-supplementation Treatment"

Yr 1 ISP 91481:134-137e
Yr 2 ISP 91481:137-139e

Your request for extension of a period of one year for the
subject protocol has been received and processed in our
office. This protocol is approved for a continuation period
of one year from the date shown above and work on the
project may continue.

Should the use of human subjects described in this protocol
continue beyond a year from the date of this notification,
it will be necessary to request an additional extension.

If you have any questions regarding this approval, please
contact the Office of Sponsored Programs at 895-1357.

cc: S. Pero (3034)
OSP File
APPENDIX B

CONSENT FORM
CONSENT TO PARTICIPATE IN A RESEARCH STUDY AT
THE SPORT INJURY RESEARCH CENTER
UNIVERSITY OF NEVADA LAS VEGAS.

Principal Investigator: Stephanie Beasley
UNLV Affiliation: Graduate Student, Department of Kinesiology
Additional Investigators: Dr. Suzanne Pero - UNLV, Dr. Todd Molnar - Southern California Orthopedic Institute, and Dr. Pat Brandner - Desert Orthopedic Institute.

TITLE OF THE STUDY:
Hyalgan versus Synvisc: A Comparison of the Functional Efficacy of Osteoarthritic Knee Joints Following Viscosupplementation Treatment.

PURPOSE:
Osteoarthritis (OA) is the most common form of arthritis that affects diarthrodic joints such as the knee. OA patients suffer from pain, stiffness and loss of function and these symptoms can range from mild to debilitating. Non-steroidal anti-inflammatory drugs (NSAIDS) have been the most common form of treatment but long term use of these drugs has been linked to toxic side effects. Currently, there is another form of treatment for OA becoming widely favored by physicians called viscosupplementation. This treatment entails directly injecting the affected joint with a product containing the viscoelastic properties lacking as a result of OA. There are only two companies currently marketing such products in the United States, Fidia S.P.A. (Hyalgan) and Biomatrix (Synvisc). The goals of the viscosupplementation products are to treat the symptoms caused by OA more efficiently and without the side effects of NSAIDS. The purpose of this study is to compare and contrast Hyalgan and Synvisc in factors such as patient perception of functional efficacy, decreased pain, decreased stiffness and the incidence of any side effects caused by either product.

PROCEDURE:
You will be receiving treatment for OA utilizing either Hyalgan or Synvisc. You have been referred to this study by Todd Molnar M.D. from the Southern California Orthopedic Institute (SCOI) or by Pat Brandner M.D. from Desert Orthopedics in Las Vegas. At your first visit with the doctor, you will receive a packet consisting of an introduction to the study and investigators, a consent form, patient information sheet, daily log sheets, and the WOMAC monthly questionnaires. You will be asked to complete the WOMAC prior to beginning your OA treatment to determine any preexisting levels of pain, stiffness, and loss of function. You will then complete the standard treatment protocol for either Hyalgan or Synvisc. You will be requested to complete a daily diary regarding your activity and levels of pain and stiffness. In addition, you will complete the WOMAC immediately upon completing the treatment protocol and then once every month for four months. All materials will be returned to the investigators upon completion of the four month study.

RISKS:
There are no perceived risks in your participation in this study.

BENEFITS:
The most important benefit of this study is to determine whether Hyalgan or Synvisc is a more effective treatment for OA, as measured by pain, stiffness, and loss of function. With this information, patients and physicians will be able to make a more educated choice regarding which treatment for OA is best for them.

College of Health Sciences
Department of Kinesiology
4505 Mary and Patton Way, Box 451004, Las Vegas, Nevada 89154-0004
702-895-0596 • FAX: 702-895-0511 • mktg.kinesiology@unlv.nevada.edu

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CONFIDENTIALITY:
All names and personal information will remain strictly confidential. Only the investigators will have access to this information.

RIGHT TO REFUSE OR WITHDRAW:
You are not obligated to participate and may withdraw from this study at any time. Non participation or withdrawal from the study will not affect your standard medical treatment by your physician.

QUESTIONS:
Any questions may be directed to your physician or to Stephanie Beasley or Dr Suzanne Pero at the University of Nevada, Las Vegas (702) 895-1289. For questions regarding your rights as a research subject, please contact the UNLV Office of Sponsored Programs at 895-1355. Signed and dated copies of this form will be retained by the physician, patient and investigators

********************
YOUR SIGNATURE BELOW CERTIFIES THAT YOU HAVE READ THE ABOVE INFORMATION AND AGREE TO PARTICIPATE IN THIS STUDY.

Participants signature       Printed name      Date

Witness' signature           Printed name      Date

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APPENDIX C

WOMAC OSTEOARTHRITIS INDEX
DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your knee joint (study joint) during the last 48 hours. By this we mean your ability to move around and to look after yourself. (Please mark your answers with an "*")

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>What degree of difficulty do you have?</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.</td>
<td>Getting in or out of the bath.</td>
</tr>
<tr>
<td>No</td>
<td>Difficulty</td>
</tr>
<tr>
<td>21.</td>
<td>Sitting</td>
</tr>
<tr>
<td>No</td>
<td>Difficulty</td>
</tr>
<tr>
<td>22.</td>
<td>Getting on or off the toilet.</td>
</tr>
<tr>
<td>No</td>
<td>Difficulty</td>
</tr>
<tr>
<td>23.</td>
<td>Performing heavy domestic duties.</td>
</tr>
<tr>
<td>No</td>
<td>Difficulty</td>
</tr>
<tr>
<td>No</td>
<td>Difficulty</td>
</tr>
</tbody>
</table>

Study Coordinator
Use Only

PFTN20
PFTN21
PFTN22
PFTN23
PFTN24

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WOMAC OSTEOARTHRITIS INDEX VERSION VA3.0

INSTRUCTIONS TO PATIENTS

In Sections A, B, and C questions will be asked in the following format and you should give your answer by putting an “X” on the horizontal line.

EXAMPLES:

1. If you put your “X” at the left of the line as shown below, then you are indicating that you have no pain.

No Pain

2. If you put your “X” at the right end of the line as shown below, then you are indicating that your pain is extreme.

Extreme Pain

3. Please note:
   a) that the further to the right you place your “X” the more pain you are experiencing.
   b) that the further to the left you place your “X” the less pain you are experiencing.
   c) please do not place your “X” past the end of the line.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have experienced in the last 48 hours.

Think about your knee joint (study joint) when answering the questionnaire. Indicate the severity of your pain, stiffness and physical disability that you feel is caused by arthritis in your knee joint (study joint).

Your study joint has been identified for you by your health care professional. If you are unsure which joint is your study joint, please ask before completing the questionnaire.
Section A

PAIN

Think about the pain you felt in your knee joint (study joint) due to your arthritis during the last 48 hours.
(Please mark your answers with an "x").

QUESTION: How much pain do you have?

1. Walking on a flat surface.
   - No Pain
   - Extreme Pain

2. Going up or down stairs.
   - No Pain
   - Extreme Pain

3. At night while in bed, i.e., pain that disturbs your sleep.
   - No Pain
   - Extreme Pain

4. Sitting or lying.
   - No Pain
   - Extreme Pain

5. Standing upright.
   - No Pain
   - Extreme Pain

Study Coordinator Use Only

PAIN1

PAIN2

PAIN3

PAIN4

PAIN5
Section B

**STIFFNESS**

Think about the stiffness (not pain) you felt in your **knee joint** (study joint) due to your arthritis during the last 48 hours.

Stiffness is a sensation of decreased ease in moving your joint.

(Please mark your answers with an "S".)

<table>
<thead>
<tr>
<th>Study Coordinator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use Only</td>
</tr>
</tbody>
</table>

6. How severe is your stiffness after first waking in the morning?

- No

- Slight

- Moderate

- Extreme

7. How severe is your stiffness after sitting, standing or resting later in the day?

- No

- Slight

- Moderate

- Extreme

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Section 6:

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your knee joint (study joint) during the last 48 hours. By this we mean your ability to move around and to look after yourself. (Please mark your answers with an "x").

<table>
<thead>
<tr>
<th>QUESTION: What degree of difficulty do you have?</th>
</tr>
</thead>
<tbody>
<tr>
<td>8. Descending stairs.</td>
</tr>
<tr>
<td>No Difficulty</td>
</tr>
<tr>
<td>Extreme Difficulty</td>
</tr>
<tr>
<td>No Difficulty</td>
</tr>
<tr>
<td>Extreme Difficulty</td>
</tr>
<tr>
<td>10. Rising from sitting.</td>
</tr>
<tr>
<td>No Difficulty</td>
</tr>
<tr>
<td>Extreme Difficulty</td>
</tr>
<tr>
<td>11. Standing.</td>
</tr>
<tr>
<td>No Difficulty</td>
</tr>
<tr>
<td>Extreme Difficulty</td>
</tr>
<tr>
<td>12. Bending to the floor.</td>
</tr>
<tr>
<td>No Difficulty</td>
</tr>
<tr>
<td>Extreme Difficulty</td>
</tr>
<tr>
<td>13. Writing on flat surface.</td>
</tr>
<tr>
<td>No Difficulty</td>
</tr>
<tr>
<td>Extreme Difficulty</td>
</tr>
</tbody>
</table>

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Study Coordinator
Use Only

PFTN8
PFTN9
PFTN10
PFTN11
PFTN12
PFTN13

End on 14. USA. v2

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DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your [knee joint] (study joint) during the last 48 hours. By this we mean your ability to move around and to look after yourself. (Please mark your answers with an "X").

QUESTION: What degree of difficulty do you have?

14. Getting in/out of car, or getting on or off a bus.
   - No Difficulty
   - Extreme Difficulty

15. Going shopping.
   - No Difficulty
   - Extreme Difficulty

16. Putting on your socks or stockings.
   - No Difficulty
   - Extreme Difficulty

17. Rising from bed.
   - No Difficulty
   - Extreme Difficulty

18. Taking off your socks or stockings.
   - No Difficulty
   - Extreme Difficulty

19. Lying in bed.
   - No Difficulty
   - Extreme Difficulty

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APPENDIX D

RAW DATA
<table>
<thead>
<tr>
<th>HP-pre</th>
<th>SP-post</th>
<th>HP-post</th>
<th>SP-post</th>
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<td>120</td>
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<td>462</td>
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<td>231</td>
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<td>287</td>
<td>31</td>
<td>62</td>
</tr>
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APPENDIX E

INDIVIDUAL SCATTERPLOT DATA
VITA

Graduate College
University of Nevada, Las Vegas

Stephanie Beasley Buford

Home Address:
4344 East Montgomery Road
Cave Creek, AZ 85331

Degrees:
Bachelor of Science, Health Education 1993
Oklahoma State University, Stillwater

Special Honors and Awards:
Dean's Honor Roll 1992-1993
Dean's Honor Roll 1997-1999

Publications:
*Stephanie Beasley Buford (formerly Stephanie Lange)

Thesis Title: A Comparison of the Functional Efficacy of Osteoarthritic Knee Joints Following Viscosupplementation Treatment.

Thesis Examination Committee:
Dr. Suzanne Pero, Ph.D., Examination Committee Chair
Dr. Mark Guadagnoli, Ph.D., Examination Committee Member
Dr. Richard Tandy, Ph.D, Examination Committee Member
Dr. Susan Silverton, M.D., Ph.D., Graduate College Faculty Representative

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