RESEARCH ARTICLE

Viscosupplementation in the treatment of osteoarthritis of the knee: Outcome and literature review

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Abstract

Background: Viscosupplementation is a recognised mode of management of osteoarthritis (OA) of the knee, especially in patients who have failed treatment with NSAIDs.
Objectives: To review the literature on viscosupplementation as well as assess its efficacy in Nigerians with OA of the knee.
Methods: Patients presenting to a private practice rheumatology clinic with symptomatic and radiographically proven OA of the knee were included, having failed two or more NSAIDs. Intra articular cross linked hyaluronan (synvisc) was given in three consecutive weekly doses. Assessment were by both patients' verbal numeric pain rating scale and physician's global pain assessment at six and twelve weeks.
Results: There was improvement in both assessments. There were few minor and transient adverse effects.
Conclusion: Viscosupplementation is both efficacious and safe in Nigerians with OA knee, as shown elsewhere.

Introduction

Osteoarthritis (OA) is the commonest type of arthritis, especially among the elderly[1]. It is responsible for considerable clinical and economic burden in the affected. OA is also associated with reduction in quality of life due to pain, as well as decreased mobility and eventual disability. The pathogenetic mechanism of OA is due to the associated progressive loss of the articular cartilage and chondrocytes within the synovial joints. These processes manifest as joint pains and eventual loss of function. An additional pathogenetic factor is the associated reduction in the concentration and molecular weight of the lubricating hyaluronic acid (hyaluronate, hyaluronan) in the synovial fluid. Such reduction leads to loss of its lubricating and shock absorbing properties. The reduction in the molecular weight of hyaluronic acid (HA) in arthritic joints has been attributed to its dilution from joint inflammatory effusions as well as presence of abnormal synoviocytes and molecular fragmentations[2-4].

Hyaluronan, as the compound sodium hyaluronate, is a highly viscous polysaccharide normally found in extracellular matrix and is a major constituent of synovial fluid and cartilage[4]. It belongs to the family of glycosaminoglycan and is composed of 1000's of repeating disaccharides units (N - acetyl glucosamine and glucuronic acid) to form a long polysaccharide chain of varying length with a high molecular weight of 5 -7 x 10^6 da. When this molecule is fully hydrated, it occupies a large spheroidal shape[4]. After synthesis in the joint by the chondrocytes and synoviocytes, HA is released into the synovial ligament and cartilage.

Synovial fluid elastoviscosity is essential for normal joint function. HA has both viscous and elastic properties, depending on the joint loading and conditions. For instance in the presence of slow and low loading, HA exhibits high viscosity with reduced elasticity. On the contrary, with increased high and fast loading, it becomes more elastic, hence acting as a shock absorber[5,6]. Apart from this viscoelasticity property, other pharmacologic properties have been identified. These include inhibition of inflammatory mediators, inhibition of phagocytic cell function, stimulation of cartilage matrix synthesis, and decreased degradation of cartilage[7-10].

On the basis of the foregoing, extrinsic HA is being increasingly used in the management of pain and stiffness for patients presenting with moderate to severe OA of the knee. This is particularly so in patients not responding or unsuitable for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). It has been recommended for the control of knee pain by both the

American College of Rheumatology (ACR) as well as the European League Against Rheumatism (EULAR). The recommendations are especially in patients with osteoarthritis of the knee and hip who have failed to respond adequately to other therapies[11-14].

Although intra-articular HA has been mostly used in OA of the knee, clinical efficacy have also been reported in OA of the hip and shoulder joints. Randomised controlled trials and open trials have shown significant decrease in pain at rest, on movement as well as functional index[15-20]. Osteoarthritis of the knee and other joints have been reported among Nigerians[21]. However there has been no documented report on the use of HA in the management of OA of the knee. The objectives of this study are to assess the efficacy of HA in Nigerian patients presenting with OA of the knee and who have failed two or more NSAIDs; as well as to review the literature.

Materials and Methods

Subjects presenting with moderate to severe knee pain to a private practice rheumatology clinic, located in Lagos, Arthrimed Specialist Clinic, were recruited into the study. These patients were seen between the period January 2009 and July 2011. The patients fulfilled the American College of Rheumatology (ACR) criteria for diagnosis of osteoarthritis of the knee. Such patients were included if they had failed to respond to at least two previous NSAIDs or narcotic analgesics such as codeine based compound and tramadol. Radiographs of both knees were requested and those fulfilling radiographic criteria for OA of the knees were included. Subjects fulfilling criteria for other diagnostic types of arthritis were excluded, even if they showed radiographic features of OA.

Standard procedure of arthrocentesis was carried out. Standard cleansing of the site of arthrocentesis was done with savlon and methylated spirit. The skin was infiltrated with lignocaine (2%) at the lateral aspect of the knee, and occasionally the medial aspect. Intra-articular hyaluronan (Synvisc Hylan GF - 20 Genzyme Corporation) was administered in weekly consecutive doses (Days 1, 8, 15). Effusions were aspirated at each visit (when present) before injecting hyaluronan. Patients were seen every two weeks for at least three months and beyond. Assessments were by a) patient's numerical pain rating on a 10 point scale with zero being 'no pain' and 10 being 'pain as bad as it can be'. b) Physician's assessment of pain as 'mild' - no pain at rest but on severe physical exertion; 'moderate' - pain on moderate physical exertion as walking up the staircase; 'severe' - pain at rest and disturbing patient's sleep. Patients were allowed rescue medications such as NSAIDs or Co-Codamol.

Results

A total of fifty patients with radiographic OA of the knees were included in the study having fulfilled the ACR criteria for OA of the knees. The demographic characteristics are as shown in Table 1. Most of the subjects were female and the mean age was 62.8 years. Both knees were involved in 41 patients (82%) while the left knee and right knee involvement were in 5 (10%) and 4 (8%) respectively. The duration of symptoms varied between 8 to 300 months with a mean of 72.9 months. Pain intensity in all patients before viscosupplementation was 8-10 by Patients Numerical Pain score and 'Moderate' to 'Severe' by the physician's global pain rating. The patient's numerical pain rating at six weeks and twelve weeks are as in Tables 2 and 3. Eleven patients were not assessed at 12 weeks as they had defaulted. More than 80% had little or no pain at both times.

Physician's global assessment of pain at onset of trial and subsequently are as shown in Tables 4, 5 & 6.

Table1: Demographic characteristics of 50 OA patients treated with viscosupplementation

Demography	Frequency (%)
Sex	
Female	41 (82)
Male	9 (18)
Female:Male	4.6:1
Age (years)	
Range	37 - 86
Mean	62.8
Median	66
Duration of symptoms (months)	
Range	8 - 300
Mean	72.9

Table 2: Patients numerical pain score at six weeks after viscosupplementation

Pain score	Frequency (%)
0-3	42 (84)
4-7	6 (12)
8-10	2 (4)

Table 3: Patients numerical pain score in 36 patients at 12 weeks after viscosupplementation

Pain score	Frequency (%)
0-3	32 (82,1)
4-7	4 (10.3)
8-10	3 (7.6)

Table 4: Physician's assessment before viscosupplementation

Physician's pain assessment	No.	(%)
None	0	
Mild	0	
Moderate	4	8
Severe	46	92

Table 5: Physician's Global pain assessment at 6 weeks

Physician pain assessment :	No.	(%)
None	38	76
Mild	8	16
Moderate	3	6
Severe	1	2

Table 6: Physician's pain assessment at 12 weeks

Pain assessment	No.	(%)
None	29	61.6
Mild	9	23.0
Moderate	3	7.7
Severe	3	7.7

Table 7: Adverse effects

Effects	No.	(%)
Post injection enthesopathy	7	14
Joint effusion	6	12
Localised reaction - pruritus	5	10
Fever	3	6
Headache	1	2

Discussion

Our study of fifty patients with radiographic OA of the knees has confirmed the usual female preponderance and the occurrence in the middle aged to elderly (Table 1). The patients numerical pain rating was in the range of 8-10 at the onset of the study but at 6 weeks, 84% had virtually no pain (0-3) with another 12% having moderate pain of 4-7, though 4% still had severe pain. The number with virtually no pain (82.1%) remain high at 12 weeks though three of the patients still rated their pain as severe (Tables 2, 3). The number assessed at 12 weeks (39 patients) was however lower consequent to default. There was also improvement in Physician's global assessment of pain between the baseline of severe pain and at both 6 and 12 weeks with 92% and 84.6% respectively having 'none' to 'mild' pain (Tables 4-6). It was difficult to follow these patients up beyond this period as the number defaulting thereafter was high. One can only assume that these patients did not come for further follow up because they were better. Adverse effects were seen in 12 cases, all of them mild. Joint effusions were the commonest, seen in six patients (Table 6) while localized transient pruritus, usually with the first injection was seen in five cases. Fever and headache were also seen. The three subjects who reported fever, one associated with the headache, could most likely have had malaria fever considering that this is endemic in Nigeria. Eleven cases presented with medial knee tendon enthesopathy usually after completion of the course of injections. Such patients, however, improved with intralesional steroid injection or local application of diclofenac. This adverse event (medial knee tendon enthesopathy) has rarely been reported in other studies. It is possible that it was present with the knee arthralgia before viscosupplementation and only came to the fore with the improvement of the knee joint pain.

Previous studies have demonstrated the efficacy and safety of intra-articular hyaluronate in the treatment of OA of the knee[15-18]. There are numerous hyaluronate preparations with different molecular weights available in medical practice. Such preparations are available either as three dose or five dose packs. These preparations include Synvisc (hylan G-F 20 Genzyme); Hyalgan (sodium hyaluronate, Sanofi - Aventis); Supartz (sodium hyaluronate, Smith and Nephew); Euflexxa (sodium hyaluronate Ferring Pharmaceuticals); Orthovisc (high molecular weight hyaluronan Depuyi Mitek).

The mode of action of hyaluronate does not seem to depend on the resident time of the compound in the synovial cavity of the knee. Exogenous hyaluronate actually begins to leave the joint within two hours of injection, though Synvisc remains up to 3 days following injection[22]. On the other hand, Supartz, Euflexxa and Orthovisc remain in the joint less than 24 hours after injection[23-25]. It has been suggested that the major effect of these agents depends on their ability, among others, to stimulate production of good synovial fluid by synovial cells and not on their resident time in the joints.

There have been conflicting reports on the role the molecular weight of hyaluronate plays in its properties of elastoviscosity in the joints. Balazcs and Denlinger[5] have suggested that increase in the molecular weight of exogenous hyaluronan increases its elastoviscosity. Other studies have however indicated otherwise [26].

Studies comparing the clinical efficacies of various preparations have reached different conclusions. For instance, Wobig and colleagues[27] have shown the efficacy of cross-linked hyaluronate (MW 800Kda). Another retrospective study comparing Synvisc (a cross-linked hyaluronate preparation) with hyaluronan (MW 615 Kda) reported statistical improvement in both preparations but also concluded that the former was superior to the latter in many parameters [28].

Major constraints in the use of these agents are their cost and availability. A dose of three injections costs about US$700. There are, however, some generics available on the Nigerian market. While they are about five times cheaper than the branded names like Synvisc, there is a dearth of studies on their efficacy and safety and most of

them depend on the data from the branded compounds. Our study has shown, that as reported in other studies, hyaluronan, Synvisc GF- 20 is an efficacious and safe agent in the treatment of knee OA especially in patients not responding to NSAIDs.

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