

Intra-articular hyaluronan injections for the treatment of osteoarthritis of the knee: A randomized, double blind, placebo controlled study

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Abstract

Objective

Hyaluronic acid (HA) polymers have been found to be useful as viscosupplements for the treatment of osteoarthritis (OA) in a number of clinical studies. It appears that HA with high molecular weights (HMW) are more effective than low molecular weight HA polymers.

Methods

A single blind, initial randomized study was conducted involving two randomly selected patient groups, which received injections of either placebo or BioHyTM, a highly purified HMW HA produced by bacterial fermentation. HA was administered intra-articularly and several functional tests, including pain level, stiffness, and physical function, were used to score efficacy at various intervals throughout the study.

Results and conclusion

The results through week 20 indicate that BioHyTM provides relief for osteoarthritic patients without causing adverse effects, although the study was not sufficiently powered to obtain statistically significant differences between the treatment groups.

Key words

BioHyTM, hyaluronan, osteoarthritis, pain, safety, viscosupplementation.

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Introduction

The sodium salt of hyaluronic acid (HA) is a naturally occurring, high molecular weight (HMW) linear polysaccharide composed of alternating residues of sodium D-glucuronate and N-acetylglucosamine. This viscoelastic polymer, often referred to as hyaluronan, is responsible for some of the protective functions of the synovial fluid, including shock absorption, traumatic energy dissipation, and lubrication, as well as controlling the migration of cells and large molecules (1, 2). In the human arthritic joint, the elasticity and viscosity of the synovial fluid are significantly lower than in the normal joint; the concentration of hyaluronan is decreased, and its molecular weight is reduced (3, 4).

The concept of viscosupplementation using HA to restore the normal rheological homeostasis of the joint was developed during the late 1960s (5). Highly elastoviscous solutions of hyaluronan were first introduced into medicine for treating inflammation in the knees of race horses (5). Replacement HA therapy in osteoarthritis (OA) patients by HMW hyaluronan increases the viscoelasticity of the synovial fluid, thus decreasing pain and conferring the better lubrication of joints. Randomized, controlled clinical trials of intra-articular hyaluronan injections for the treatment of osteoarthritis of the knee have shown variable results. Some of these trials suggest long lasting pain relief (6-8), while others have failed to show a difference between hyaluronan and placebo (9, 10). Today, several products comprising HA with molecular weights varying from 0.5 to 6 million Daltons (MDa) are commercially available. The HMW HA preparations for intra-articular administration have greater pain reducing effects in OA joints than the low molecular HA preparations (11-13).

BioHy™ is a highly purified, non-inflammatory, high molecular weight (3.0 ± 0.6 MDa) sodium hyaluronate manufactured by bacterial fermentation of the non-hemolytic strain of *Streptococcus zooepidemicus*. In this feasibility study, we assessed the tolerability and efficacy of BioHy™ in a small,

placebo-controlled group of patients with OA of the knee.

Patients and methods

Patients

Outpatients of the orthopedic clinic Assaf Harofeh Medical Center (Zerifin, Israel) fulfilling the following inclusion criteria were enrolled in the study: adults of either sex, between the ages of 60 and 85, with evidence of idiopathic symptomatic clinical OA of the knee as classified according to the Altman criteria (14) and radiologically verified OA of the knee (stages 2-4) according to the Kellgren and Lawrence grading system (15), but otherwise in good general health as determined by a complete medical history and physical examination, with no previous history of surgical treatment of the joint or of arthroscopy or injections to the knee in the 6 months prior to initiation of the study. Analgesic or NSAIDs medications were not deprived before or during the trial.

Patients with the following conditions were excluded from the study; patients with knee OA originating from an intra-articular fracture, rheumatoid arthritis, joint infection, other inflammatory and metabolic arthritis, or OA of the hip joint; patients with significant systemic diseases, allergy or atopy, or skin conditions overlying the joint which could cause the administration of injections to be problematic; and patients with copious joint exudates (i.e., more than 15 milliliters of aspirated synovial fluid) because large amounts of exudates could have an effect on the active substance by dilution.

All patients were fully briefed and signed an informed consent form prior to participating in the study. Patients were withdrawn from the study if compliance was inadequate. Concurrent and escape medication, including non-steroidal anti-inflammatory agents or paracetamol, were allowed throughout the study. The use of medication was equally divided between the groups.

Study design

The study was an open label, prospective, single blinded, randomized, placebo-

bo controlled trial and was approved by the Ethical Review Board of the Assaf Harofeh Medical Center, Israel.

Treatment administration

Treatment consisted of 20 mg BioHy™ (10 mg/ml) a highly purified, sodium hyaluronate with an average molecular weight of 3.0 ± 0.6 MDa, manufactured via bacterial fermentation. BioHy™ was supplied as a sterile 1% solution in 2 ml phosphate buffered saline, pH 6.5 - 7.5. The placebo consisted of 2 ml of the phosphate buffered saline. BioHy™ and the placebo were allocated randomly to two parallel groups, which received 5 weekly injections of either the active substance (BioHy™) or the placebo preparation. Before injection any knee effusion was aspirated and its volume was noted and tested for appearance, polymorphonuclear cells and white blood cells. In order to maintain single blind conditions and eliminate the risk of bias, the physician who performed the clinical assessment was different from the one responsible for handling and injection.

Clinical assessment

The patients underwent clinical assessment on a weekly basis during the first 4 weeks, then at weeks 6, 12 and 20. This included pain level at rest and during activity, stiffness, and physical function as assessed by the Musculoskeletal Outcomes Data Evaluation and Management System (MODEMS) arthritic module. The level of pain was assessed while the patient stood upright, was in a sitting or lying position, walked on a step incline, walked on a flat surface, or at night in bed. Categorical scoring (none = 1, mild = 2, moderate = 3, severe = 4, extreme = 5) was used in the assessment (16). In addition, muscle strength, stiffness, and tenderness of the knee joint upon palpation were monitored and scored using the same scale. Active range of motion was assessed on each visit, and the scores were classified as 1 = more than 135; 2 = 90-135; 3 = 45-90; and 4 = less than 45.

Laboratory assessment

Laboratory assessment, blood chem-

istry and hematology (according to standard methods) were performed only at baseline in the hospital's laboratory.

Statistical analysis

A general linear model (GLM) was used to account for the demographic variability in age at baseline. The primary endpoint was pain score, and secondary efficacy endpoints included stiffness and physical function. Each endpoint consisted of a subset of questions which were assessed using categorical scoring. Differences between the two treatment groups were evaluated after calculating the average of each parameter for each visit and the change in the main score at post-treatment visits from screening. Analysis was determined by the status of OA of the knee. The pair-wise t-test was performed on changes observed at post-treatment visits from the condition observed during screening.

Results

Forty-nine patients with idiopathic OA were enrolled in the study. Twenty-five patients received BioHy™ and 24 received placebo. Table I summarizes their characteristics at the start of the trial. There was no statistically significant difference between these parameters in the two groups.

The majority of patients were classified as stage 3 with a definite narrowing of the joint space (15), 64% in the BioHy™ group and 44% in the placebo group. In both groups, 21% were categorized as stage 2 with possible narrowing of the joint space. Patients categorized as stage 4, with a marked nar-

rowing of the joint space, included 28% from the placebo group and 12% from the BioHy™ group. Six patients did not receive all 5 intra-articular injections, 3 in the placebo group and 2 in the BioHy™ group.

Three patients from the BioHy group withdrew prematurely; one had severe pain due to trauma from the needle, one due to subsequent total knee replacement, and one patient was lost to follow-up. Four patients in the placebo group did not complete the study; 3 of them wished to withdraw, and one was lost to follow-up.

Synovial fluid aspiration was performed in only 5 patients and the laboratory analysis was only partially available.

Performance assessment

This feasibility study showed that BioHy™, injected intra-articularly, is well tolerated and does not cause unexpected local side effects. All pain parameters were assessed and scored by the investigator.

Pain while working on a flat surface. Figure 1 A shows the change in the mean categorical score assigned by the investigator during the 20 weeks of the study. In general, during the course of treatment BioHy administration was associated with decreased pain while walking on a flat surface, although the differences between treatment groups were not statistically significant.

Pain while walking on steps or while standing upright. The pain experienced by the patients in both treatment groups while performing these activities was similar for each task (data not shown).

Pain at night while in bed: Figure 1 B

Table I. Baseline characteristics of the patients.

Sex (%)	BioHy™ (n = 25)	Placebo (n = 24)	Total (n = 49)
Male	6 (24)	7 (29)	13
Female	19 (76)	17 (71)	36
Age (yrs.)	71	70	71
Stage 2	6	5	11 ^a
Stage 3	16	11	27
Stage 4	3	7	10

^a one patient was undefined with regard to the initial state of his disease.

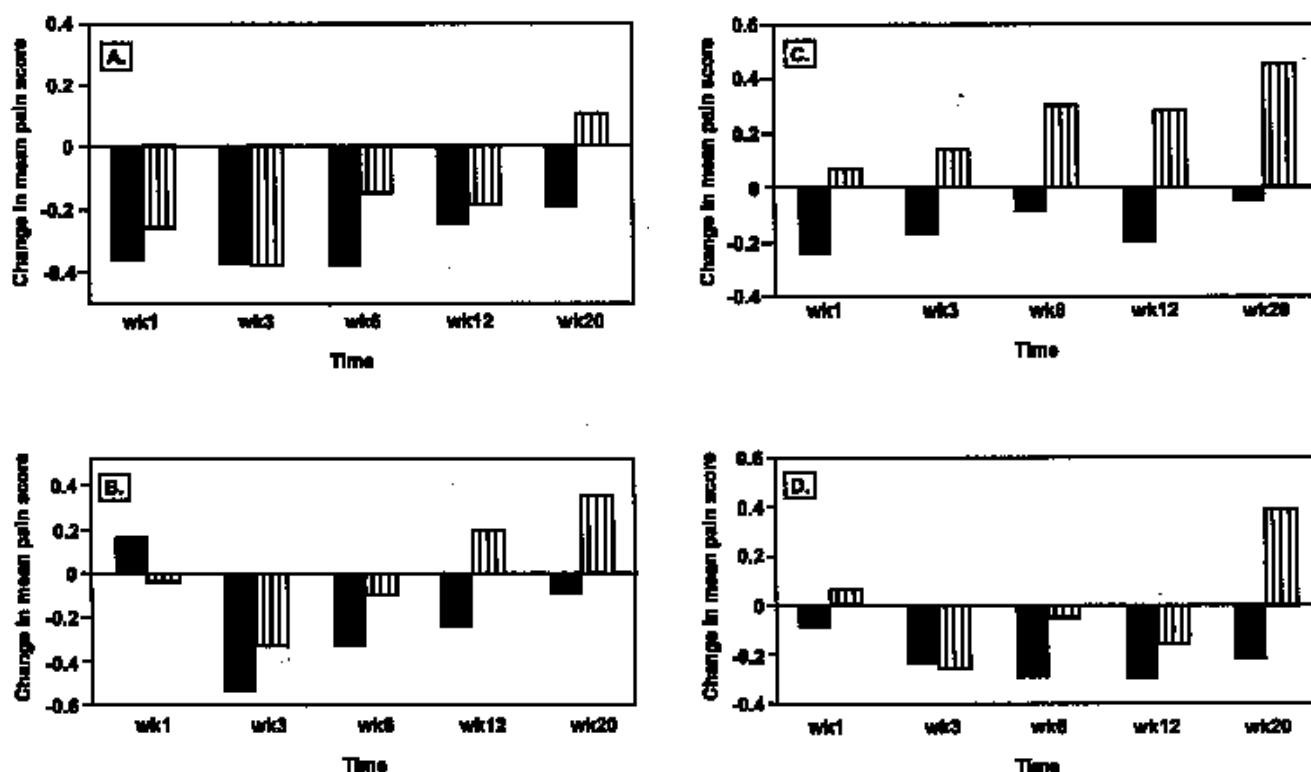


Fig. 1. BioHy effects on knee pain.

The pain experienced by each patient was assessed, while he was: (a) walking on a flat surface; (b) at night while in bed; or (c) sitting or lying down. The extent of knee pain, according to the MODEMS scoring system, was evaluated for each patient before treatment and at the indicated time points following the first treatment. The difference between pain assessment values at the first visit and subsequent visits was calculated, and the mean values for each group were subsequently calculated for all of the patients. An average of all of the assessed scores was calculated for each treatment group at each time point, and these results appear in (d). The results for the BioHy-treated patients are represented by the dark bars, and those for the placebo-treated control patients are represented by the lighter bars.

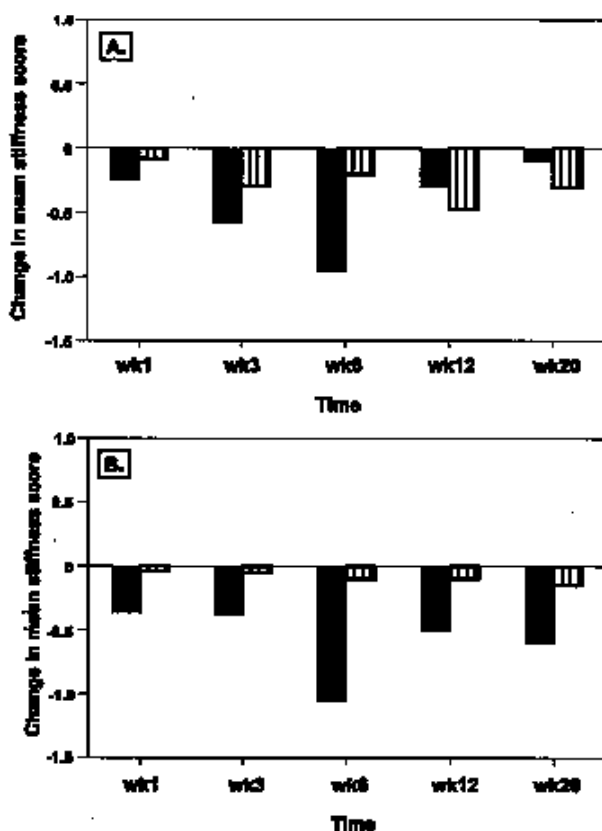


Fig. 2. BioHy effects on knee stiffness.

The stiffness experienced by each patient was assessed, after he: (a) rose in the morning; or (b) sat, rested, or was lying down. The extent of stiffness, according to the MODEMS scoring system, was evaluated for each patient before treatment and at the indicated time points following the first treatment. The difference between stiffness assessment values at the first visit and subsequent visits was calculated, and the mean values for each group were subsequently calculated for all of the patients. The results for the BioHy-treated patients are represented by the dark bars, and those for the placebo-treated control patients are represented by the lighter bars.

shows the change in mean categorical score assigned by the investigator during the 20 weeks of the study period. In general, during the course of treatment BioHy administration was associated with decreased pain at night while in bed after the second injection, which continued to decrease through week 20. This figure shows that the disparity between the average responses of the treatment groups increased during the course of the study. However, the differences between treatment groups for these parameters were also not statistically significant.

Pain in the sitting or lying position. Figure 1 C shows the change in mean categorical score assigned by the investigator throughout the 20 weeks of the study period. The improvement in pain experienced when sitting or lying down fluctuated. However, there was a distinct trend of improvement for patients treated with BioHy™, and the disparity between the average responses of the treatment groups also increased during the course of the study with regard to this parameter. The composite effect was sustained throughout the duration of the study, to week 20.

Taken cumulatively, the results for the BioHy™ treated patient group showed a distinct positive trend in the average of all 5 pain parameters assessed in comparison to the placebo group (Fig 1 D).

Knee joint tenderness upon palpation. The initial levels of joint tenderness were similarly distributed among the patients in the placebo and BioHy treatment groups at screening. During visits 1-6, progressively more BioHy-treated patients felt relief, while the maximal relative number of placebo-treated patients feeling some relief was essentially reached at the second visit. The greatest relief for both groups was observed at visit 6 (week 12). During this visit, 64% of the BioHy-treated patients were found to have experienced some relief, while 46% of the placebo-treated patients experienced some relief according to the scoring with this parameter.

Stiffness at the knee joint. Stiffness of the knee joint was assessed by both the severity of stiffness after walking in the

morning, and the severity of stiffness after sitting, lying or resting (Figs. 2A and 2B). Both of these parameters indicated a trend, suggesting that BioHy™ may decrease stiffness when the knee is moved after rest.

Muscle strength: No difference was observed in the patients' capability to perform daily tasks. In addition, examination of quadriceps power during subsequent visits showed a progressive tendency for the BioHy™ group to achieve a very good score, while the overall score of patients receiving the placebo did not vary from the score at screening.

Safety

No systemic adverse effects were recorded which could be related to the treatment. Twenty-nine patients (18 who received the drug and 11 the placebo) complained of knee pain immediately after the injection which was related to the injection procedure and not to the HA. One patient who received BioHy had knee pain immediately after the injection which was related to the injection procedure and not to the treatment. One patient who received BioHy had knee pain and swelling 2 weeks after injection number 5. The duration of the event was several days, and it resolved spontaneously. Synovial fluid analysis in this patient showed low WBC and protein levels.

Discussion

The current body of evidence indicates that HA injections provide beneficial effects for patients with osteoarthritis of the knee. There are several possible mechanisms for this beneficial effect. In the synovial fluid, a reduction in HA size appears during joint inflammation and may be indicative of reduced lubrication. However, the involvement of other mechanisms in the disease etiology is also possible. This may partially explain the results of various clinical studies, in which it is not clear that HA always functions as a treatment for these disorders, since the disorders also resolved themselves in a portion of the placebo-treated individuals, while in some of the HA-treated patients the

disorder persisted. In any case, these treatments are apparently rarely accompanied by adverse reactions. The recorded adverse reactions are local and seem to be related to the manner in which HA is injected rather than to an effect of HA, itself. Therefore, HA products such as BioHy, which consistently contain high molecular weight HA, may be beneficial for patients with various inflammatory joint disorders without causing serious side effects.

The current body of evidence indicates that HA injections provide beneficial effects for patients with joint disorders (17). This clinical investigation is the first study designed to treat osteoarthritis that involves an ultra pure HA produced by bacterial fermentation. BioHy™ comprises a 1% physiological solution in a phosphate buffered saline of high molecular weight HA (3 ± 0.4 MDa), with a limiting viscosity of 100,000 cps at room temperature. As such, the active substance has particularly high viscoelastic properties, and the purity of the product is carefully controlled by cGMP manufacturing conditions, so that in contrast to the rooster comb preparation, protein contamination levels are insignificant. The same HA preparation, marketed under the name of BioLon, has been safely and successfully used for a number of years in cataract surgery in many countries including European Union countries and the United States.

The end points of clinical studies involving patients with osteoarthritis primarily involve pain and the functioning of the joint. In the present study, BioHy-treated patients on average experienced progressive relief at rest or when performing normal activities which required stress on the treated joint, as the study progressed from week 0 to week 12. They also experienced less knee stiffness after periods of inactivity during this period. By comparison, the average responses of placebo-treated patients were generally unchanged during this evaluation period. Though these changes were not statistically different, and the small sample size and free allowance for taking pain medication interfered in the evaluation of the treatment, the performance of BioHy

suggested a favorable trend in decreasing pain. This feasibility study also showed that the intra-articular injection of BioHy™ is well tolerated, and no HA-related adverse events were found. A similar performance has been found after viscosupplementation with rooster comb-derived HA products and in more powered studies their usefulness in decreasing pain and improving joint functioning in OA patients was clearly demonstrated (18). Moreover, it was shown that there are clinical advantages to administering a higher molecular weight HA product (11-13). Synvisc is a chemically cross-linked 6 MDa HA polymer derived from rooster combs, and its effect was compared with those of two medium MW HA-derived products (0.75 MDa and 2 MDa). While Synvisc performed significantly better than the 0.75 MDa polymer, no statistical differences between the effects of the higher MW products were found. Therefore, HA products such as BioHy™, which consistently contain high molecular weight HA, may be beneficial for patients with various inflammatory joint disorders without causing serious side effects. BioHy will be examined in further studies involving greater numbers of patients in order to show statistically significant clinical effectiveness.

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