A single-blind, placebo-controlled study of glycosaminoglycan-peptide complex ('Rumalon') in patients with osteoarthritis of the hip or knee

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Summary

A randomized, single-blind, placebo-controlled trial was carried out in 62 patients (30 with osteoarthritis of the hip, 32 with osteoarthritis of the knee) to examine the efficacy of glycosaminoglycan-peptide complex in the treatment of osteoarthritis. Patients received 8-week courses of trial medication, each consisting of intramuscular injections of 3×2 ml ampoules per week, alternating with 8-week periods free of trial medication, in addition to conventional drug therapy and physiotherapy, as required. After 2-years' treatment, glycosaminoglycan-peptide-treated patients showed significant improvements, as compared with placebo, in relation to night pain, pain during the day, joint mobility and walking ability. Similar results were seen with both osteoarthritis of the hip and knee. In osteoarthritis of the knee it was also possible to assess joint swelling and this also showed a significant improvement. There were no significant changes in range of joint movement except for a significant decrease in active flexion in the patients with osteoarthritis of the knee treated with placebo. In contrast with many anti-osteoarthritic drugs, glycosaminoglycan-peptide complex was very well tolerated. These results suggest that glycosaminoglycan-peptide complex may be a valuable alternative form of long-term therapy for patients with osteoarthritis.

Key words: Glycosaminoglycan-peptide complex – osteoarthritis

Introduction

Osteoarthritis is primarily a destructive disease of articular cartilage probably beginning with metabolic abnormalities of the proteoglycans and collagen network.[3,5] Catabolic processes predominate over the anabolic processes and, on balance, there is a loss of glycosaminoglycans from the matrix. As a consequence, the cartilage slowly loses its mechanical properties such as elasticity and compressibility. The condition is associated with an impairment of the synovial fluid, which

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is responsible not only for joint lubrication but also for the supply of nutrients and the removal of catabolic breakdown products. Capsular and synovial changes also occur.

The ideal aim of treatment, either with drugs (antirheumatics and analgesics) or by physiotherapy or other means, is to return the decompensated and activated osteoarthritis state to a latent phase. Truly effective therapy would have to restore the impaired cartilage metabolism to normal, i.e. slow down the disordered metabolism of the chondrocytes and restore the correct composition of the proteoglycans, so as to arrest or, ideally, to reverse the natural progression of the pathological process. An effective preparation should stimulate the specific synthetic functions of the chondrocytes and block the pathological enzymatic breakdown processes in the cartilage matrix. Further requirements would be some degree of restoration of the damaged joint cartilage and protection against mechanical or chemical cartilage damage.

No therapy with proven ability to reverse the osteoarthritic process is yet available. The alternative approach to therapy is to relieve symptoms and improve function in spite of a continuing pathological deterioration. Analgesic or anti-inflammatory drugs, combined with physical therapy, provide some help, but are far from perfect.

A glycosaminoglycan-peptide complex from bovine cartilage and bone marrow ('Rumalon'†) has been found in several animal models relevant to human osteoarthritis to produce positive effects such as improvement in symptoms (weight bearing)[13] or inhibition of progression of cartilage lesions.[4,8,11,12] Direct or indirect effects of glycosaminoglycan-peptide complex on 'lymphokines modulation' can be deduced from *in vitro* results,[7,10,14] but their transferability and relevance with respect to the human osteoarthritic process still need more research. It is possible, however, that the symptomatic and 'anti-osteoarthritic' effects can be explained by the regulation of chondrocyte metabolism and the increase of chondrocyte vitality already experimentally proven *in vivo*.[2]

The clinical benefit of glycosaminoglycan-peptide complex in human osteoarthritis of the hip or knee was demonstrated by objective radiological and outcome measures in two long-term trials by Rejholec.[15] Further trials in osteoarthritis of the hip and/or knee support these findings.[1,6,9]

Glycosaminoglycan-peptide complex has been shown to have a potential chondroprotective effect in *in vitro* and *in vivo* models, as well as providing probable symptomatic relief and long-term benefits in human osteoarthritis. However, relatively few controlled studies have been performed, and metabolic effects in osteoarthritic subjects have not yet been explored.

The aim of the present study was to evaluate the effect of glycosaminoglycan-peptide complex in patients with osteoarthritis of the hip and knee.

Patients and methods

Seventy patients were recruited into the study. To be acceptable for the trial, they were required to be in the age range 40 to 70 years and to be suffering from

†trade mark, Robapharm

primary painful osteoarthritis of the hip or knee, with radiological narrowing of the joint space not exceeding two-thirds of the normal space, and with no radiological deformity of the joint surfaces. Patients were excluded if they had non-osteoarthritic joint disease, secondary osteoarthritis, advanced disease requiring high-dose drug therapy, or if they had received more than 24 ml glycosaminoglycan-peptide complex during the previous year. They were also excluded if they were pregnant, if they were suffering from severe cardiac, hepatic, renal or haematological disease, or insulin-dependent diabetes mellitus, or if they were considered to be potentially unreliable. All selected patients gave their informed consent to participate in the trial.

The trial was of a randomized, single-blind design. On entry to the trial and on completing initial assessments, trial medication was commenced. According to a randomization code, each patient was allocated to receive either glycosaminoglycan-peptide complex ('Rumalon') or placebo. In all cases, treatment consisted of 3 courses of intramuscular injections per year. Each course consisted of 24×2 ml injections, administered over an 8-week period at the rate of 3 injections per week (given on separate days), with intervals of approximately 8 weeks between courses. Each patient, therefore, received a total of 144 ml per year for the 2 years of the trial. During the trial period, patients were allowed to receive analgesics, non-steroidal anti-inflammatory drugs and physiotherapy as required, although they were not permitted to take such drugs for a period of at least 36 hours prior to each assessment. All concomitant therapy received during the trial period was recorded.

Assessments were performed at trial entry and at 6-monthly periods thereafter. The degree of pain was assessed using a 10 cm visual analogue scale, separately for pain during the day and night pain. The limitation in joint mobility was assessed by a 4-grade scale (0=none, 1=slight, 2=moderate, 3=severe/disabling). Hyperaesthesia was rated according to a 4-grade scale (0=none, 1=mild, 2=moderate, 3=severe). The walking time for 10 metres was determined and the range of (active and passive) joint movement was determined. Any adverse reactions to therapy were determined by asking non-leading questions.

The administration of trial medication was stopped prematurely only if necessitated by the occurrence of side-effects. In cases where the efficacy of trial medication appeared inadequate, it was continued but was supplemented by other therapy as required.

The significance of differences between and within the two treatment groups was examined using Student's t-test, Wilcoxon-Mann-Whitney-U-Test or Wilcoxon Test, as appropriate. The threshold for significance was taken as $p=0.05$.

Results

Seventy patients entered the trial; 62 of these (30 with osteoarthritis of the hip, 32 with osteoarthritis of the knee) completed the full trial period and were available for evaluation. Eight patients dropped out, 2 because of adverse effects, 2 because of lack of efficacy and 4 because of being lost to follow up.

Patients with osteoarthritis of the hip

There were 30 evaluable patients with osteoarthritis of the hip, 19 of whom received glycosaminoglycan-peptide complex and 11 of whom received placebo. The two groups were well matched as regards age, sex, weight, height, duration of disease and age at onset of disease, with no significant differences between groups with respect to any of these demographic and clinical features (Table I).

Table I. Details of patients with osteoarthritis of the hip: number and mean (±S.D.) values

Patients	Glycosaminoglycan-peptide complex	Placebo
No. studies	19	11
Sex: Male	2	2
Female	17	9
Age (years)	58.2±7.46	56.8±6.31
Weight (kg)	72.4±11.52	69.2±10.61
Height (cm)	161.6±9.72	162.4±11.60
Age at onset of disease (years)	55.2±7.52	54.2±6.32
Duration of disease (years)	3.13±4.87	2.71±1.65

At the start of the study, there were no significant differences between the groups as regards the various indices of disease that were assessed (Tables II and III).

Pain intensity (night and day) and joint mobility were reduced after treatment to milder categories in the glycosaminoglycan-peptide complex group in a statistically significant manner (Table II). In the placebo-treated group there were no significant differences after treatment in these parameters, except for daytime pain. In all of these 3 parameters, statistically significant differences could be found between the two groups. The duration of walking time for 10 metres was also reduced significantly in the glycosaminoglycan-peptide complex but not in the placebo group. There were no significant differences with respect to the ranges of active or passive joint movements (Table III).

Table II. Assessment of pain parameters at the start and at the end of treatment: mean (±S.D.) scores for patients with osteoarthritis of the hip

Assessment	Glycosaminoglycan-peptide complex (n=19)		Placebo (n=11)	
	Before treatment	After treatment	Before treatment	After treatment
Night pain	2.4±2.9	0.4±0.69	2.1±1.58	1.9±0.83
	← p<0.01 →			
	← p<0.001 →			
Day pain	4.5±1.12	1.3±1.16	5.0±1.18	3.1±1.22
	← p<0.001 →		← p<0.01 →	
	← p<0.01 →			
Joint mobility	1.7±0.73	0.5±0.84	1.8±0.40	1.4±0.67
	← p<0.001 →			
	← p<0.005 →			

Table III. Measurement of joint function and walking ability at the start and at the end of treatment: mean (±S.D.) values in patients with osteoarthritis of the hip

Measurement	Glycosaminoglycan-peptide complex (n=19)		Placebo (n=11)	
	Before treatment	After treatment	Before treatment	After treatment
Joint flexion (°):				
Active	122.3±13.56	123.8±10.45	128.5±10.74	129.7±10.53
Passive	132.5±11.86	130.3±10.86	137.3±12.12	137.8±12.52
Walking time for 10 metres (sec)	21.8±6.88	18.0±4.86	24.1±7.31	23.9±3.30
	← p<0.05 →			
		← p<0.001 →		

Patients with osteoarthritis of the knee

There were 32 evaluable patients with osteoarthritis of the knee, 13 of whom received glycosaminoglycan-peptide complex and 19 of whom received placebo. Both groups were well matched with respect to age, sex, weight, height and age at onset of disease, with no significant differences between the groups with respect to any of these features (Table IV). There was an appreciable mean difference in disease duration (mean 6.5 years in the glycosaminoglycan-peptide complex group vs 4.2 years in the placebo group, Table IV), although this difference was not statistically significant.

Table IV. Details of patients with osteoarthritis of the knee: number and mean (±S.D.) values

Patients	Glycosaminoglycan-peptide complex	Placebo
No. studied	13	19
Sex: Male	2	5
Female	11	14
Age (years)	55.8±9.17	56.5±8.21
Weight (kg)	68.5±9.90	72.7±11.33
Height (cm)	158.6±4.99	164.2±10.05
Age at onset of disease (years)	49.4±8.05	52.3±8.52
Duration of disease (years)	6.48±7.60	4.17±3.06

At the start of the trial, there were no significant differences between the groups with respect to any of the assessment indices except for joint mobility (Tables V and VI). Within the glycosaminoglycan-peptide complex group, there was statistically significant improvement from baseline status with respect to night pain, pain during the day, joint mobility, hyperaesthesia, the number of patients with swelling, and walking time (Tables V and VI). A statistically significant difference between the two groups was detected in all these parameters at the end of the study.

There were no significant differences between the two ranges with respect to ranges of active or passive joint movement (Table VI). The placebo group showed a significant decrease in active flexion after treatment.

Table V. Assessment of pain parameters at the start and at the end of treatment: mean (±S.D.) scores in patients with osteoarthritis of the knee

Assessment	Glycosaminoglycan-peptide complex (n=13)		Placebo (n=19)	
	Before treatment	After treatment	Before treatment	After treatment
Night pain	2.8±1.83	0.8±0.83	3.3±1.95	2.2±1.72
	← p<0.001 →			
	← p<0.01 →			
Day pain	5.2±1.59	1.3±1.25	5.2±1.26	3.0±1.94
	← p<0.001 →		← p<0.001 →	
	← p<0.01 →			
Joint mobility	1.7±0.75	0.5±0.66	2.2±0.54	1.9±1.10
	← p<0.005 →			
	← p<0.05 →			
	← p<0.001 →			
Hyperaesthesia	1.1±0.76	0.2±0.38	0.9±0.81	0.7±0.81
	← p<0.002 →			
	← p<0.05 →			
Patients with swelling: number (%)	7 (54%)	0 (0%)	12 (63%)	9 (47%)
	← p<0.05 →			
	← p<0.005 →			

Table VI. Measurement of joint function and walking ability at the start and at the end of treatment: mean (±S.D.) values in patients with osteoarthritis of the knee

Measurement	Glycosaminoglycan-peptide complex (n=13)		Placebo (n=19)	
	Before treatment	After treatment	Before treatment	After treatment
Joint flexion (°):				
Active	66.2±11.39	65.2±16.81	72.6±16.95	68.0±18.09
			← p<0.05 →	
Passive	58.1±11.64	56.8±18.82	63.0±17.78	59.4±18.28
Walking time for 10 metres (sec)	21.1±7.58	16.0±3.21	23.2±9.73	22.1±8.29
	← p<0.002 →			
	← p<0.02 →			

Tolerance

Glycosaminoglycan-peptide complex was well tolerated and no adverse experiences were reported during treatment by any of the patients. Five patients on placebo reported headache and gastro-intestinal upsets.

Discussion

The present study confirms the experience of other investigators that glycosaminoglycan-peptide complex ('Rumalon') is effective in the basic treatment of osteo-

arthritis of the hip and knee and is also well tolerated.[15] It is important to note that the significant subjective improvements, i.e. pain, joint mobility, were also confirmed by significant improvements in more objective criteria, such as joint swelling and walking ability. The same improvements were not seen in the placebo group, in spite of the use of concurrently-administered non-steroidal anti-inflammatory drugs and physiotherapy as required.

Whilst it is obvious from the results of this and other studies that glycosaminoglycan-peptide complex is effective in providing effective symptomatic relief in osteoarthritic patients, its mode of action has not been fully established yet. It may well be, therefore, that other effects on cartilage metabolism, which have been demonstrated experimentally,[2] may play a significant role in the long-term treatment of degenerative joint diseases such as osteoarthritis of the hip or knee. Further long-term clinical studies are necessary to confim this. In the mean time, it would appear that glycosaminoglycan-peptide complex ('Rumalon') offers not only an effective but also a well-tolerated form of treatment which can be used to replace or supplement non-steroidal anti-inflammatory drugs, particularly in long-term therapy.

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