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OSTEOARTHRITIS and CARTILAGE

Efficacy and tolerability of oral chondroitin sulfate as a symptomatic slow-acting drug for osteoarthritis (SYSADOA) in the treatment of knee osteoarthritis

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Summary

Patients with osteoarthritis (OA) of the knee were treated with chondroitin sulfate (CS, Condrosulf®, IBSA, Lugano, CH) in a randomized, double-blind, placebo-controlled study, performed in two centres.

The efficacy and tolerability of oral CS capsules 2×400 mg/day vs placebo was assessed in a 6-month study period. Patients with idiopathic or clinically symptomatic knee OA, with Kellgren and Lawrence radiological scores I–III, were included in this trial. Clinical controls were performed at months 0, 1, 3 and 6.

Eighty patients completed the 6-month treatment period. Lequesne's Index and spontaneous joint pain (VAS) decreased constantly in the CS group; on the contrary, slight variations of the scores were reported in the placebo group. The walking time, defined as the minimum time to perform a 20-meter walk, showed a statistically significant constant reduction only in the CS group. ANOVA with repeated measures showed a statistically significant difference in favor of the CS group for these three parameters. During the study, patients belonging to the placebo group reported a higher paracetamol consumption, but this consumption was not statistically different between the two treatment groups. Efficacy judgements were significant in favor of the CS group. Both treatments were very well tolerated.

All these results strongly suggest that chondroitin sulfate acts as a symptomatic slow-acting drug in knee OA.

Key words: Chondroitin sulfate, Knee osteoarthritis, SYSADOA.

Introduction

The symptomatic osteoarthritic knees could be treated either conservatively, including physical and pharmacologic possibilities, or surgically. For a long period of time the analgesics and the nonsteroidal anti-inflammatory agents were the only solution in the pharmacologic treatment of these disorders, but due to recent developments the current concept is changing. According to Lequesne [1] the pharmacologic possibilities in the treatment of osteoarthritic patients fall into three categories:

1. Analgesics and non-steroidal anti-inflammatory agents;
2. Symptomatic slow-acting drugs for osteoarthritis (SYSADOA);
3. Chondroprotective or truly disease-modifying agents (not available as yet).

The aim of this study was to determine, whether 800 mg oral chondroitin sulfate (CS, Condrosulf®, IBSA, Lugano, CH) (SYSADOA), having been given for 6 months, was effective in the treatment of knee osteoarthritis.

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Design of the study

The study was designed to be a randomized double-blind, placebo-controlled study involving two centers, to include at least 80 patients, suffering from knee osteoarthritis [2]. It was performed during the period from September 1995 to September 1996 in Hungary, Budapest.

Patients and methods

Hospitalized or out-patients with idiopathic or secondary clinically symptomatic knee OA for more than 6 months, and showing upon entry Kellgren and Lawrence radiological score I–III were enrolled in the study [2–3].

All patients suffering from other inflammatory diseases or systemic conditions affecting or possibly involving the joints as well as patients with secondary osteoarthritis of the knee joint were excluded from the study [3].

The chondroitin sulfate and the placebo were

Table I
Patients' characteristics

Group	CS ($n=39$)	PBO ($n=46$)	P values
Age (m ± S.D.)	60.6 ± 9.6	59.4 ± 9.0	0.557*
range	41 ÷ 83	39 ÷ 74	
Sex (M/F)	17/22	17/29	0.657†
Weight in kg (m ± S.D.)	83.4 ± 13.9	80.2 ± 16.1	0.343*
range	57 ÷ 115	51 ÷ 110	
Height in cm (m ± S.D.)	169 ± 9	166 ± 9	0.126*
range	154 ÷ 190	152 ÷ 194	

*Student's t-test.
†Fisher exact test.

administered in exactly the same way, with the same dosage (800 mg/day) for a period of 6 months.

The following clinical evaluation parameters were recorded at entry and then at month 1, 3 and 6 (end of the trial):

- Spontaneous joint pain was evaluated, considering pain during physical daily activity. The intensity of pain was judged by the patient on a Visual Analogue Scale (VAS) of 100 mm [4];
- Paracetamol consumption [5]. In case of pain, patients were free to take paracetamol if it was required. The consumption was registered as total number of tablets taken during the study period.
- Locomotor capacity, measuring the walking time [6]. The time required to take a 20-meter walk on flat ground was measured at each visit.
- Lequesne's Index, summarizing the algofunctional parameters concerning the pain, the maximal walking distance, the discomfort in daily life movements (score from 0 to 24), showing the exact pain evolution [5].
- Global efficacy and tolerability judgement by patients and by physicians as well [7, 8]. The treatment global efficacy was judged at month 6 by the investigator and by the patient, using a 4-point scale: excellent = 3, good = 2, fair = 1, poor = 0.

The statistical analysis of the results was performed by an independent Institute of Biostatistics (IBIS Informatica S.r.1., Milan, Italy) using BMDP Statistical Software. Analysis of variance with repeated measures and multiple comparisons according to Bonferroni test was used for the parametric variables. Nonparametric variables and variables that were not normally distributed were analyzed with the Mann–Whitney test, while the Pearson chi-square test was used for analyzing the categorical type of variable. In the case of tables 2×2 the Fisher exact test was utilized.

All the statistical tests were computed as two-tailed, and only results with $P < 0.05$ were considered as significant.

Results

PATIENTS' CHARACTERISTIC

A total of 85 patients, aged between 39 and 83, were included in the statistical analysis, and the ratio according to sex, age, body weight and size is shown in Table I. Eighty of them (36 chondroitin sulfate, CS/44 placebo, PBO) completed the 6-month treatment period, while five patients (three CS + two PBO) dropped out after 3 months, three of them (two CS + one PBO) failing to turn up for follow-up examination; one (CS) had severe viral infection, and one (PBO) had brain tumor surgery, both not correlated to the treatment. The two groups were statistically homogeneous to

Table II
Kellgren and Lawrence radiological score

	Femorotibial right (TR)		Femorotibial left (TL)		Femoropatellar right (PR)		Femoropatellar left (PL)	
X-ray score	CS ($n=39$)	PBO ($n=46$)	CS ($n=39$)	PBO ($n=46$)	CS ($n=39$)	PBO ($n=46$)	CS ($n=39$)	PBO ($n=46$)
0	11	5	7	11	35	43	34	45
I	10	12	10	10	2	2	2	1
II	14	20	19	17	1	1	3	0
III	4	9	3	8	1	0	0	0
Chi-square test	$P=0.181$		$P=0.438$		$P=0.740$		$P=0.115$	

Table III
Distribution of affected knees

	CS ($n=39$)	PBO ($n=46$)
Monolateral	17	16
Bilateral	22	30

Fisher exact test: P = 0.504.

compare. The distribution of radiological score for femorotibial right (TR) or left (TL) and femoropatellar right (PR) or left (PL) at baseline is listed in Table II. The homogeneity between treatment groups was confirmed by the chi-square test for each site analyzed (TR, TL, PR, PL). In addition, we arbitrarily calculated a total Kellgren and Lawrence radiological score for each patient as follows. Total radiological score = radiological score (TR + TL + PR + PL). The total mean radiological score was 3.13 ± 2.07 for the CS group and 3.30 ± 1.41 for the PBO group, respectively.

The Mann-Whitney test was used to compare these mean values and no significant difference was observed between groups ($P=0.247$).

Also, the distribution of affected knees in monolateral or bilateral knee OA (Table III) did not show any statistically significant difference between the CS and PBO groups (Fisher exact test: $P=0.504$).

SPONTANEOUS JOINT PAIN (VAS)

The degree of spontaneous joint pain measured with the Huskisson Visual Analogue Scale (VAS) [4] showed a constant significant reduction of spontaneous joint pain in the CS group, but not in the PBO one. The two groups were homogeneous at baseline (ANOVA: P = ns). After 1 month of treatment, there was a 23% decrease of joint pain in the CS group as compared to 12% in the PBO group. This difference increased further at month 3 with an overall decrease in the CS group of 36% vs 7% in the PBO group. At the end of the study the reduction of joint pain was of 43% in the CS group vs 3% in the PBO group. The difference between both groups was statistically significant in favor of the CS group from month 3 on (ANOVA with repeated measures and multiple comparisons according to Bonferroni test: $P < 0.01$) (Table IV and Fig. 1).

PARACETAMOL CONSUMPTION

During the 6-month study, patients belonging to the placebo group reported a higher paracetamol consumption than those in the CS group, but the difference between groups at different times was not statistically significant (Mann-Whitney test: P = ns). In Table IV the mean, median and range monthly paracetamol consumption is also reported.

Since this pathology showed different symptoms according to the patient, a great variance in the paracetamol consumption was justified.

LOCOMOTOR CAPACITY–WALKING TIME

The walking time, defined as the minimum time (sec) to perform a 20-metre walk on flat ground, showed a significant difference between the two groups in favor of the CS at month 6 and a statistically significant constant reduction of walking time was reported only in the CS group. Table IV reports the results of the ANOVA with repeated measures and multiple comparisons according to Bonferroni test.

LEQUESNE'S INDEX

The functional status of the patients in their daily lives was evaluated using Lequesne's Index [5]. This clinical study foresaw the inclusion of patients with mono- or bilateral knee osteoarthritis and, if it was possible, the Lequesne's Index was arbitrarily evaluated for each affected knee, left or right, separately. To start with, the distribution of the scores for the Lequesne's

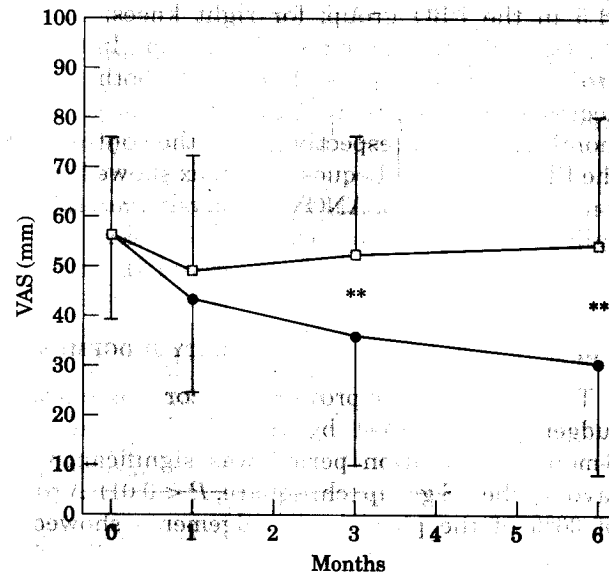

FIG. 1. VAS, spontaneous joint pain (in mm). $^{**}P < 0.01$ (ANOVA with repeated measures and multiple comparisons according to Bonferroni test). –●– = CS; –□– = PBO.

Table IV
Efficacy results (mean values ± S.D.) (CS: $n = 39$; PBO: $n = 46$)

Evaluation parameters			Control visits (months) 0	1	3	6
VAS (mm)	CS		56 ± 17	43 ± 19‡	36 ± 26‡ **	32 ± 23‡ **
	PBO		56 ± 20	49 ± 23	52 ± 24	55 ± 26
Walking time (sec)	CS		25.3 ± 7.5	23.3 ± 6.5	23.2 ± 7.2†	22.5 ± 6.8‡ *
	PBO		25.1 ± 8.3	24.8 ± 8.2	24.5 ± 7.9	25.0 ± 7.9
Lequesne's Index						
Left knee	CS		12.0 ± 3.7	10.2 ± 4.0‡	9.0 ± 4.5‡ *	7.6 ± 4.2‡ **
	PBO		11.5 ± 4.1	10.6 ± 4.2	10.7 ± 4.3	11.1 ± 4.6
Right knee	CS		12.8 ± 3.6	10.8 ± 3.8‡	9.9 ± 4.6‡	8.1 ± 4.7‡ **
	PBO		11.8 ± 3.9	10.9 ± 3.8	10.2 ± 4.0‡	10.3 ± 4.8
				Study period (months) 0–1	1–3	3–6
Monthly paracetamol consumption	CS	Mean ± S.D.		7.6 ± 12.4	7.5 ± 10.7	5.6 ± 7.0
		Median		2	2.5	3
		Range		0 ÷ 48	0 ÷ 51	0 ÷ 25
	PBO	Mean ± S.D.		11.4 ± 22.5	10.8 ± 20.0	10.3 ± 12.7
		Median		5	4.5	5.5
		Range		0 ÷ 125	0 ÷ 116	0 ÷ 61

ANOVA with repeated measures and multiple comparisons according to Bonferroni test:
within group (basal vs control time): † = $P < 0.05$; ‡ $P < 0.01$
between groups: * = $P < 0.05$; ** $P < 0.01$
The Mann–Whitney test between groups was utilized for the mean monthly paracetamol consumption.

Index was homogeneous in the two groups with no statistically significant difference between groups (for left knees: 12 in the CS group vs 11.5 in the PBO group; for right knees: 12.8 in the CS group vs 11.8 in the PBO group). In the CS group, the Lequesne's Index for both knees decreased constantly by about 15, 24 and 37%, at month 1, 3 and 6, respectively. On the contrary, in the PBO group the Lequesne's Index showed slight variations of scores. ANOVA analysis was statistically highly significant in favor of the CS group for both knees (Table IV and Figs 2 and 3).

GLOBAL EFFICACY AND TOLERABILITY JUDGEMENT

The subjective improvement score of efficacy judgement expressed by the physician after a 6-month observation period was significantly in favor of the CS group (chi-square, $P < 0.01$). A total of 36% of the physician's judgements showed a global efficacy of the PBO treatment as nil vs 8% of the CS group. In addition, the physician's evaluation was in 26% of the cases in favor of the CS group 'very good' and in 43% 'good', while only 9% of the physician's judgement concerning the PBO group reached 'very good' results and 23% showed 'good' results. The same criterion expressed by the patients also showed a positive

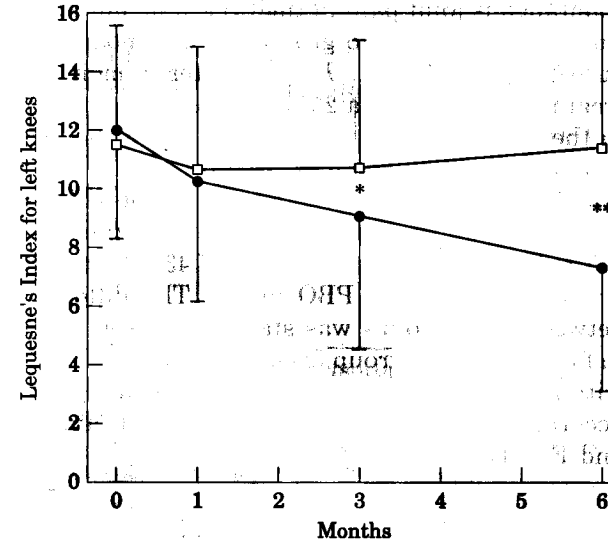

FIG. 2. Lequesne's Index for left knees (mean values). *$P < 0.05$, **$P < 0.01$ (ANOVA with repeated measures and multiple comparisons according to Bonferroni test). —●— = CS; —□— = PBO.

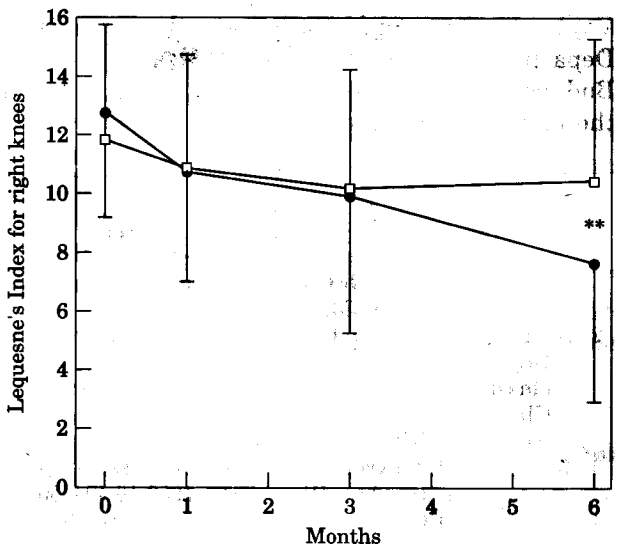

FIG. 3. Lequesne's Index for right knees (mean values). $^{**}P < 0.01$ (ANOVA with repeated measures and multiple comparisons according to Bonferroni test). —●— = CS; —□— = PBO.

trend for the CS group (chi-square, $P < 0.01$). At month 6, patients of the CS group expressed 26% very good results, 40% good results and 23% fair results, and 11% reported an absence of improvement. In contrast, the PBO patients expressed 18% of excellent results, 14% good results and 29% fair results, but an absence of improvement was found in 39% of patients (Table V).

The overall tolerability judgement of the test drug expressed both by the physician and the patients was excellent. Only one patient of the PBO group complained of flight gastrointestinal symptoms after 1 month, probably correlated to the treatment. The comparison between both groups after a 6-months treatment period did not show any significant difference in terms of clinical side-effects. In addition, the biological tolerability was also excellent in both groups.

Conclusions

This 6-month randomized, double-blind, placebo-controlled-study, involving two centers, including 85 patients of both sexes, aged 39–83 years, suffering from knee osteoarthritis, was designed to evaluate the clinical efficacy and tolerability of the oral administration of 800 mg chondroitin sulfate. The functional status of the patients in their daily life was evaluated using the Lequesne's Index. In the chondroitin sulfate group, the Lequesne's Index decreased constantly by about 15, 24 and 37%, at month 1, 3 and 6, respectively. On the contrary, in the placebo group the Lequesne's Index showed slight variations of the scores. Also, the walking time, defined as the minimum time (sec) to perform a 20-meter walk on flatground, showed a constant reduction of time only in the CS-group. Both parameters proved the improvement of joint mobility in the CS group.

Considering the remission of the joint pain measured with the VAS (Huskisson Visual Analogue Scale) in the CS group, the lower paracetamol consumption in this group and the excellent tolerability of the chondroitin sulfate, we may affirm that CS can safely alleviate OA symptoms showing an antalgic activity. The very good tolerability of CS is of great importance, especially when dealing with chronic clinical states such as osteoarthritis which require prolonged treatments or at least periodic treatment cycles.

Even if the aim of this clinical trial was just to prove the efficacy of CS in patients suffering from knee OA, were calculated the statistic again twice:

- by considering the x-ray severity of patients at inclusion time.
- by dividing patients in monolateral or bilateral knee OA.

Neither of these two statistical results differed from those obtained with the intention-to-treat analysis as reported above.

Table V
Global efficacy judgments (%)

	Physician				Patient			
Groups	Very good	Good	Fair	Poor	Very good	Good	Fair	Poor
PBO	9	23	32	36	18	14	29	39
CS	26	43	23	8	26	40	23	11
Chi-square test	$P < 0.01$				$P < 0.01$			

In conclusion, the following effects are proven by this study concerning the chondroitin sulfate CS vs placebo PBO:

- CS was able to reduce pain significantly;
- CS reduced the walking time significantly;
- CS reduced the Lequesne's Index significantly;
- There was a significantly positive global efficacy judgement for CS;
- The overall tolerability judgement was excellent.

The final results of this study demonstrate that chondroitin sulfate given orally for 6 months at a dosage of 800 mg/day is an effective and safe symptomatic slow-acting drug (SYSADOA) in patients suffering from knee osteoarthritis, and that its efficacy seemed to be independent from the x-ray severity of the pathology and its location (monolateral or bilateral).

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