Comparison of the Antiinflammatory Efficacy of Chondroitin Sulfate and Diclofenac Sodium in Patients with Knee Osteoarthritis

PIETRO MORREALE, ROBERTO MANOPULO, MICHELE GALATI, LUCIANO BOCCANERA, GIORGIO SAPONATI, and LUIGI BOCCHI

ABSTRACT. ***Objective.*** To assess the clinical efficacy of chondroitin sulfate (CS) in comparison with the non-steroidal antiinflammatory drug (NSAID) diclofenac sodium (DS) in a medium/longterm clinical study in patients with knee osteoarthritis (OA).

Methods. This was a randomized, multicenter, double blind, double dummy study. 146 patients with knee OA were recruited into 2 groups. During the first month, patients in the NSAID group were treated with 3 × 50 mg DS tablets/day and 3 × 400 mg placebo (for CS) sachets; from Month 2 to Month 3, patients were given placebo sachets alone. In the CS group, patients were treated with 3 × 50 mg placebo (for diclofenac) tablets/day and 3 × 400 mg CS sachets/day during the first month; from Month 2 to Month 3, these patients received only CS sachets. Both groups were treated with 3 × 400 mg placebo sachets from Month 4 to Month 6. Clinical efficacy was evaluated by assessing the Lequesne Index, spontaneous pain (using the Huskisson visual analog scale), pain on load (using a 4 point ordinal scale), and paracetamol consumption.

Results. Patients treated with the NSAID showed prompt and plain reduction of clinical symptoms, which, however, reappeared after the end of treatment; in the CS group, the therapeutic response appeared later in time but lasted for up to 3 months after the end of treatment.

Conclusion. CS seems to have slow but gradually increasing clinical activity in OA; these benefits last for a long period after the end of treatment. (*J Rheumatol 1996;***23:1385–91**)

Key Indexing Terms:
KNEE OSTEOARTHRITIS
CLINICAL EFFICACY
CHONDROITIN SULFATE
GLUCOSAMINOGLYCANS

Osteoarthritis (OA) is a degenerative pathology primarily affecting the articular cartilage that leads to periodic acute inflammation.

The articular cartilage consists of a cellular component (the chondrocytes) distributed in an amorphous matrix that is produced by the chondrocytes themselves. This matrix is made up of collagen and elastic fibers immersed in a mucoid substance (chondromucoid) and is essentially made up of glycoproteins and proteoglycans. Proteoglycans are complexes formed by a protein backbone with lateral branching of sulfated mucopolysaccharides (chondroitin sulfates A and C and keratan sulfate). Due to the presence of the carboxylic and sulfate groups, the glucosaminoglycans, and chondroitin sulfate (CS) in particular, constitute an ordered and strongly electronegative structure with high water retention power. This guarantees the resistance and elasticity of the cartilage itself[1].

Although the primary cause of the osteoarthritic process is not clear, it has been ascertained that a metabolic alteration of the chondrocytes takes place in the first phases of the degenerative sequence, resulting in a disturbance of the ground substance with a disorganization of its components and a reduction of the water content[2-4]. In addition, elastase, a proteolytic enzyme present in leukocytes, intervenes in the degradation of collagen and proteoglycans, thus contributing to the tissue damage[5].

It has been demonstrated that, besides being a fundamental constituent of the cartilaginous matrix[6], CS is able to cause an increase in RNA synthesis by the chondrocytes, which appears to correlate with an increase in the synthesis of proteoglycans and collagens[7-10]; in addition, there is evidence to indicate that CS partially inhibits leukocyte elastase activity[11-14].

There is strong evidence that this substance is effective on the inflammatory and algofunctional status of OA, as shown in animals and in humans. Indeed, a 6 month CS treatment at a daily dose of 1200 mg in gonarthritic[15] and coxarthritic patients[16] showed good efficacy, improving the symptomatology and the functional variables significantly,

From the Clinical Institute of Orthopaedics and Traumatology, University of Siena, the Orthopaedic and Traumatology Division, S. Orsola–Malpighi Hospital, Bologna, and ISPharm, Lucca, Italy.

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P. Morreale, MD, Assistant, Orthopaedic and Traumatology Division, University of Siena; R. Manopulo, MD, Consultant; M. Galati, MD, Assistant; L. Boccanera, Professor, Orthopaedic and Traumatology Division, S. Orsola-Malpighi Hospital; G. Saponati, MD, Clinical Research Chief Executive, ISPharm; L. Bocchi, Professor, Clinical Institute of Orthopaedics and Traumatology, University of Siena.

Address reprint requests to Dr. G. Saponati, c/o Research and Development Department, IBSA, Via al Ponte 13, 6903 Lugano, Switzerland.

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compared to a placebo group. A significant difference has also been noticed concerning the consumption of antiinflammatory drugs and analgesics during the observation period. A 3 month treatment with CS in a patient group with retro-patellar chondropathy gave the same results[17]. In all studies the drug was very well tolerated.

These data convinced us that it was advisable to test the efficacy of CS as pharmacological treatment of OA.

MATERIALS AND METHODS

Patients. Two centers participated in this 6 month, randomized, double blind, parallel group study. The sample size was estimated to be 80 patients/group. Patients of either sex, between 40 and 75 years of age, with grade I or II (preservation of the articular space) monolateral or bilateral knee OA (femorotibial OA), who had stopped taking antiinflammatory and/or chondroprotective treatment for at least 15/30 days, respectively, before the start of the study, were eligible for the trial.

The selected patients were kept under observation for 5 days; they were provided with paracetamol (500 mg tablets) in case of pain and were asked to record the number of tablets taken per day (in a patient's diary).

Patients with peptic gastroduodenal ulcers, diabetic diseases, renal dysfunction, hypertension, or known hypersensitivity to the test preparations were excluded from the study. Pregnant and lactating women were also excluded.

All patients gave their informed consent to participate in the study, which was carried out in accordance with the Helsinki Declaration and its subsequent amendments.

Test drugs, dosage, and administration. To preserve the double blind condition of the study, the diclofenac sodium (DS) tablets and placebo tablets (for DS) were ground and inserted into capsules of identical appearance. CS granules and the placebo granules (for CS) were available in sachets of identical appearance. During the first month of the study, patients assigned to the CS group took CS (one 400 mg sachet, 3 times a day) and placebo for DS (one capsule, 3 times a day); from Month 2 to Month 3 only CS sachets were prescribed. Patients assigned to the DS group took DS capsules (one 50 mg capsule, 3 times a day) and placebo granules for CS (one sachet, 3 times a day) for the first month of the study; during Months 2 and 3, patients were treated with placebo sachets alone. Both groups of patients took placebo sachets during the 3 subsequent months (Months 4, 5, and 6). Patients who did not take study medication for more than 80% of the total prescribed duration (6 months) were regarded as "noncompliant." During the 6 month study period, patients were allowed to take analgesic (paracetamol 500 mg tablet) if necessary and the daily consumption was recorded.

Visit schedule and assessments. Patients underwent control visits at entry (Day 0), every 10 days during the first month of treatment (Days 10, 20, 30) and then after 45, 60, 90, 120, and 180 days. At entry, a complete clinical history was recorded for each patient and each was examined. Laboratory tests were performed at entry and on Day 90. At each visit the investigators used the Lequesne Index[18] (Table 4) to assess treatment efficacy. Spontaneous pain was assessed using the 100 mm Huskisson visual analog scale (VAS)[19], while pain on load was assessed using a 4 point ordinal scale (pain: absent, light, moderate, intense). The average consumption of paracetamol tablets (secondary variable) was also evaluated (patients kept a diary to record the number of tablets taken per day). Patient compliance to treatment was estimated at each control visit by counting the number of capsules and sachets used from the packs of drug distributed to patients at the previous visit. A 4 point ordinal scale was used to estimate compliance (3 = excellent, i.e., drug consumption > 90%; 2 = good, drug consumption 81–90%; 1 = fair, drug consumption 65–80%; 0 = poor, drug consumption < 65%). At the end of the study, the investigators were asked to express a global judgment on the patient's response to therapy. All adverse drug events were recorded, regardless of causality, and the type, duration, severity, and outcome were described.

Statistical methods. Statistical analysis was performed by Dr. F. De Vathaire, Institut Gustave-Roussy, Villejuif, France. The analysis of variance was used for the Lequesne Index, spontaneous pain, pain on load, and intake of paracetamol. This was followed by the multiple Bonferroni t test. The minimum level of significance was set at 0.05. To test for statistically significant intergroup differences, the Mann-Whitney U test was used for categorical variables, while the 2 tailed independent Student's t test was used for continuous variables.

RESULTS

A total of 146 patients were included in this study. Demographic data for patients are given in Table 1. At baseline, the groups were well balanced for sex, age, and severity of disease. The number of withdrawals and the rates and reasons for dropping out were similar in both groups (Table 1). Twenty patients withdrew from the study prematurely. Of these, 9 were from the CS group, 11 from the DS group. Fifteen of these 20 patients (7 from the CS group, 8 from the DS group) withdrew for logistic reasons; 3 patients (one from the CS group, 2 from the DS group) dropped out because either the physician or the patient felt the treatment did not provide sufficient therapeutic effect. Two patients (one from each group) dropped out due to severe gastrointestinal side effects. Hence, data from 126 of the 146 patients enrolled (65 CS group; 61 DS group) were analyzed for efficacy.

Efficacy. The groups were homogeneous at baseline for the Lequesne Index score, spontaneous pain, pain on load, and paracetamol intake. The mean values at the different controls are reported in Table 2.

Lequesne Index. At the start of the study, the mean scores for the Lequesne Index were very similar in both treatment groups: 7.83 in the CS group and 7.93 in the DS group (Table 2, Figure 1). Both treatments caused a sharp decrease in this score, with a far greater decrease observed in the DS group compared with the CS group. At the end of the one

Table 1. Demographic data and clinical characteristics according to rheumatoid factor status.

	CS group	DS group	p
No. of patients at entry	74	72	
Men/Women	31/43	29/43	NS
Age (Mean ± SD), yrs	55.39 ± 12.21	56.37 ± 12.08	NS
Severity of disease			
I degree	33	35	NS
II degree	41	37	
Withdrawals			
Adverse GI effect	1	1	NS
Lack of effect	1	2	
Other	7	8	
Total	9	11	
No. of patients completed	65	61	

NS: not significant.

Table 2. Mean values, standard deviation of Lequesne Index, Huskisson VAS, pain on load, intake of paracetamol, and compliance. Variations in percentage compared to the basal value are in parentheses.

	Entry	Day 10	Day 20	Day 30	Day 45	Day 60
Lequesne Index						
CS	7.8±3.5	7.7±3.3 (-1.93)	6.5±2.8 (-16.44)	4.9±2.5 (-37.52)	3.3±2.2 (-58.03)	2.3±2.3 (-70.60)**
DS	7.9±3.7	6.9±3.5 (-13.43)	4.1±2.9 (-47.93)**	2.9±2.8 (-62.60)**	2.9±2.3 (-63.43)	4.1±3.1 (-48.76)
Huskisson (VAS)						
CS	56.4±16.6	48.5±14.6 (-14.0)	39.3±13.3 (-30.3)	30.9±14.0 (-45.2)	23,7±13.6 (-57.9)	16.6±12.8 (-70.6)
DS	56.7±18.7	46.7±18.2 (-17.6)	36.6±15.9 (-35.5)	30.0±15.0 (-47.1)	24.0±11.7 (-57.7)	20.5±9.7 (-63.8)
Pain on load						
CS	2.5±0.5	2.3±0.5 (-5.62)	1.8±0.6 (-25.63)	1.4±0.6 (-43.75)	1.1±0.7 (-56.25)	0.6±0.7 (-75.63)**
DS	2.5±0.59	2.1±0.7 (-17.11)	1.4±0.6 (-44.08)**	1.0±0.7 (-59.21)**	0.9±0.7 (-61.84)	1.1±0.7 (-54.61)
Intake of paracetamol						
CS	1.0±0.4	0.9±0.4 (-14.00)	0.7±0.6 (-26.00)	0.3±0.5 (-68.00)	0.4±0.6 (-62.00)	0.1±0.3 (-88.00)
DS	1.2±0.8	0.6±0.7 (-46.55)*	0.3±0.6 (-75.86)**	0.4±0.6 (-67.24)	0.3±0.6 (-72.41)	0.6±0.8 (-51.72)
Compliance						
CS	2.54 ± 0.5	2.5±0.5 (0.79)	2.8±0.4 (9.45)	2.8±0.4 (10.24)	2.8±0.4 (9.45)	2.8±0.4 (11.81)
DS	2.40 ± 0.5	2.6±0.5 (9.17)	2.7±0.4 (13.33)	2.8±0.5 (15.83)	2.8±0.4 (16.67)	2.8±0.4 (16.67)

	Entry	Day 90	Day 120	Day 150	Day 180
Lequesne Index					
CS	7.8±3.5	1.7±2.2 (-77.95)**	1.7±2.3 (-78.34)**	2.2±2.4 (-71.57)**	2.8±2.2 (-64.41)**
DS	7.9±3.7	4.9±3.2 (-37.81)	5.6±3.6 (-29.75)	5.8±3.5 (-26.86)	6.1±3.4 (-22.52)
Huskisson (VAS)					
CS	56.4±16.6	11.5±12.1 (-79.6)	9.4±9.7 (-83.3)**	9.7±8.3 (-82.8)**	10.4±9.5 (-81.6)**
DS	56.7±18.7	18.9±13.0 (-66.7)	22.9±13.6 (-59.6)	28.4±14.0 (-49.9)	36.2±16.1 (-36.1)
Pain on load					
CS	2.5±0.5	0.4±0.6 (-84.37)**	0.5±0.7 (-80.63)**	0.8±0.7 (-66.88)**	1.1±0.5 (-53.12)**
DS	2.5±0.59	1.3±0.7 (-48.68)	1.6±0.7 (-36.18)	1.7±0.7 (-30.26)	2.0±0.5 (-21.05)
Intake of paracetamol					
CS	1.0±0.4	0.1±0.4 (-88.00)**	0.3±0.5 (-70.00)**	0.4±0.5 (-62.00)**	0.8±0.6 (-20.00)**
DS	1.2±0.8	0.7±0.8 (-37.93)	1.1±0.9 (-5.17)	1.4±0.8 (18.97)	1.7±0.8 (43.10)
Compliance					
CS	2.54 ± 0.5	2.7±0.4 (7.09)	2.7±0.5 (5.51)	2.7±0.5 (6.30)**	2.4±0.5 (-3.94)
DS	2.40 ± 0.5	2.7±0.5 (11.67)	2.5±0.5 (2.50)	2.2±0.4 (-6.67)	2.2±0.4 (-10.00)

* $p < 0.05$ between the 2 groups.
**$p < 0.01$ between the 2 groups.

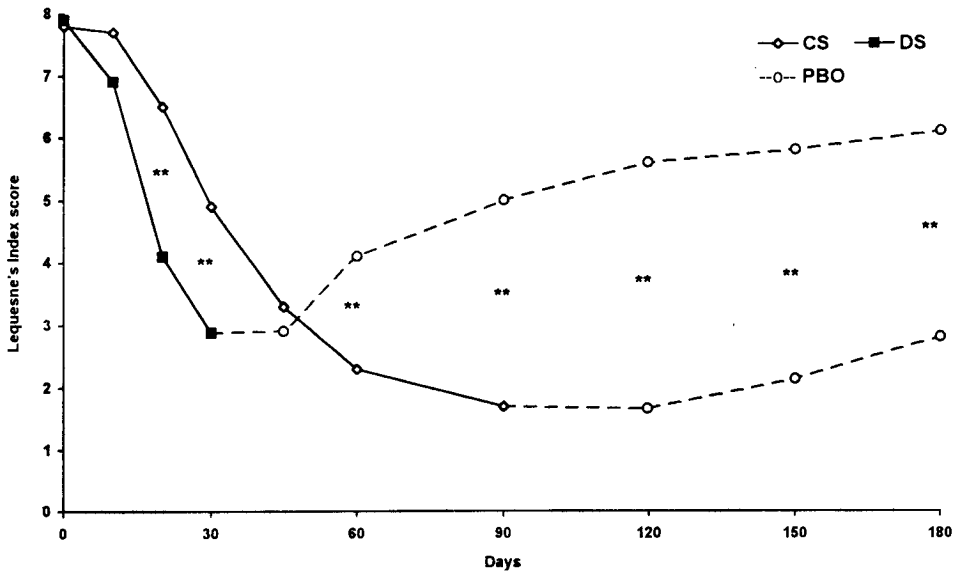

Figure 1. Mean values of Lequesne Index during the study. *p < 0.05, **p < 0.01 between groups. PBO: placebo.

month treatment period with diclofenac, the difference between the 2 groups was still significant in favor of the DS group ($p<0.01$).

After this one month treatment period, there was a definite stabilization of the Lequesne Index score in the DS group, which was treated with placebo alone during Months 2 and 3 of the study, whereas a constant decrease was observed in the CS group treated with CS also during Months 2 and 3. On Day 45, the Lequesne Index scores were similar in both groups (p = not significant). From this time onward, the scores increased sharply in the DS group, while a continuous decrease was observed in the CS group. On Days 60 and 90 of the study the difference in favor of the CS group was highly significant. At the end of the 90 day treatment period with CS there was a 78.0% reduction in scores, while at the end of the 30 day treatment period with diclofenac the reduction was 62.6%. During Months 4, 5, and 6, when patients in both groups took placebo sachets daily, the Lequesne Index score increased in both groups: in the CS group this increase took place slowly over these 3 months and the difference with the DS group was significant ($p<0.01$) at each control time. At the end of this period, the score in the CS group was 64.4% lower than baseline levels, while in the diclofenac group this value was 29.7% lower than baseline levels.

Spontaneous pain. This variable showed a progressive and significant decrease ($p<0.01$) in both groups with a similar trend to Day 60 (Table 2, Figure 2); it must be noted that the intake of paracetamol was higher in the CS group during this period. Over the subsequent period, the mean values for spontaneous pain decreased considerably in the patients treated with CS (-82% at the 6 month control compared with baseline values), while patients treated with diclofenac showed a progressive increase in mean values (-36% at the end of the study), which resulted in a statistically significant difference between the groups during the last 4 months of the observation period.

Pain on load. Pain on load was measured using a 4 point ordinal scale (from 0 = no pain to 3 = severe pain). This variable showed similar behavior to the Lequesne Index (Table 2, Figure 3); that is, during the first month of treatment, there was greater reduction in pain on load in the DS group compared with the CS group.Yet it must be pointed out that the difference between treatments was less definite in this period compared with the Lequesne Index. At baseline the mean value for pain on load was very similar in both groups, 2.46 in the CS group, 2.49 in the DS group. During the first 30 days of the study, there was a 43.8% reduction in the CS group and a 59.2% reduction in the diclofenac group. During the 90 day treatment period with CS there was an 84.5% reduction in pain on load in the CS group. In the 3 month period after the end of pharmacological treatment, during which the patients received placebo, there was an increase in the pain on load that was substantially parallel in both groups; at the end of this 3 month period, the reduction in the CS group was 53.1% compared with baseline values, whereas in the DS group the reduction was 36.18%.

Intake of paracetamol. Paracetamol consumption correlated with the improvements in the Lequesne Index and pain on load (Table 2, Figure 4). During the first month of treatment the reduction of paracetamol consumption was more evident in the DS group than in the CS group when evaluated at Days 10 ($p<0.05$) and 20 ($p<0.01$). However, at Day 30 the reduction in paracetamol consumption was very similar in

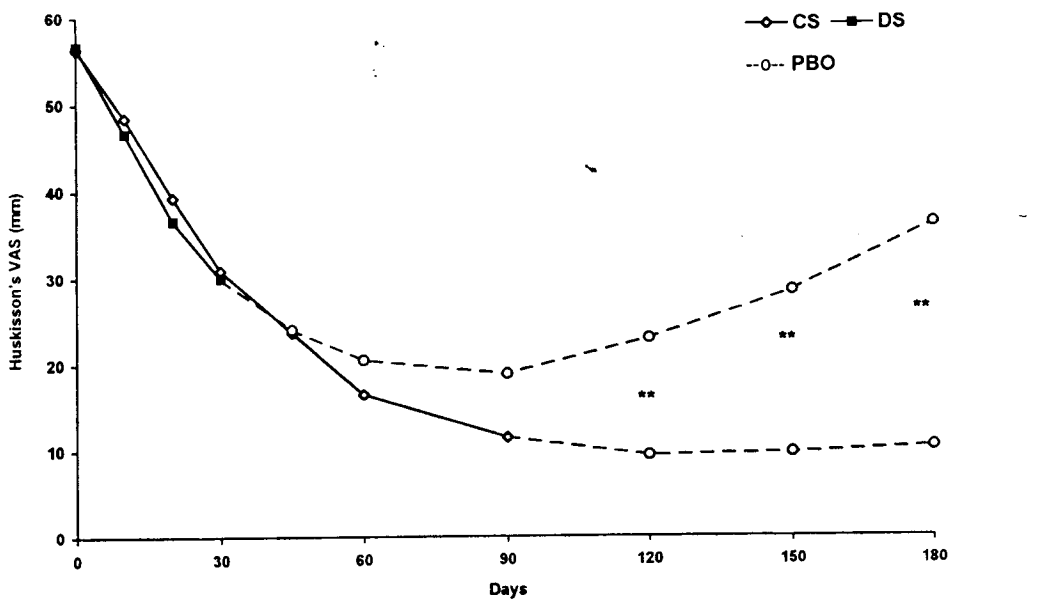

Figure 2. Mean values of Huskisson VAS. *p < 0.05, **p < 0.01 between groups.

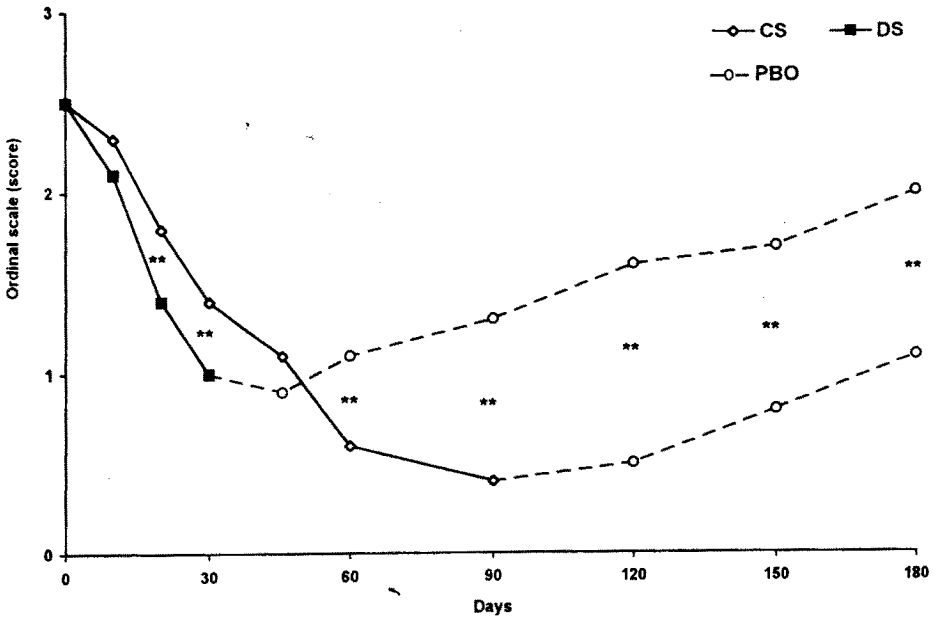

Figure 3. Mean values of pain on load. * $p < 0.05$, ** $p < 0.01$ between groups.

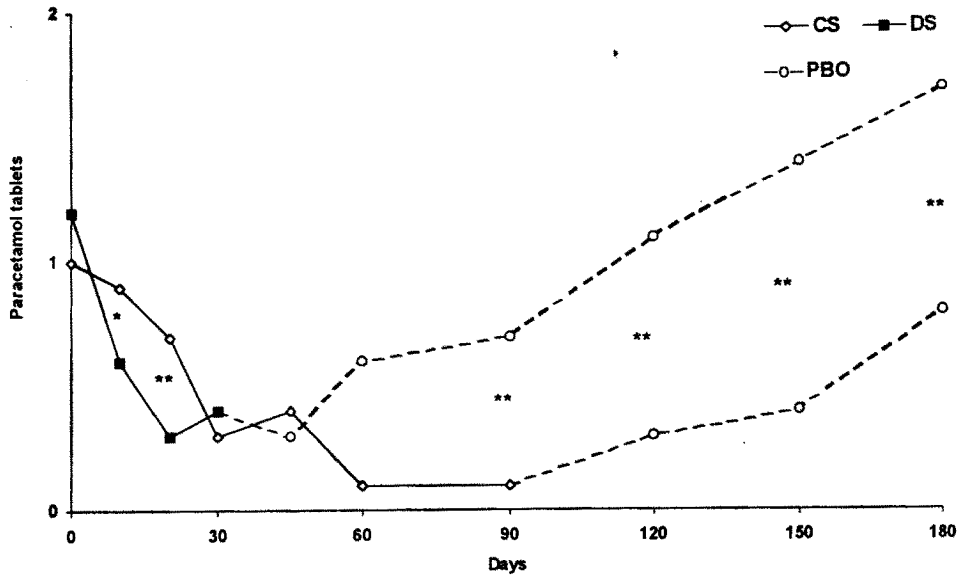

Figure 4. Mean number of paracetamol tablets used by patients. * $p<0.05$, ** $p<0.01$ between groups.

both groups (-68.0% in the CS group, -67.2% in the DS group; p = not significant). At the end of treatment with CS (Day 90) there was an 88.0% reduction in paracetamol consumption, compared with baseline values, while with DS group the reduction was 37.8% ($p<0.01$ between the 2 groups).

In this case also, the treatment interruption and replacement by placebo resulted in an increase in paracetamol consumption. Three months after treatment interruption, analgesic consumption in the DS group was 5.2% lower than baseline levels, whereas in the CS group it was 20% lower.

Global assessment of efficacy. The physician's overall efficacy assessment at the end of the study was significantly in favor of the CS group compared to the DS group ($p<0.01$) (Table 3).

Compliance. As expected, compliance showed an opposite trend to that of the previously analyzed variables, that is, it increased during the period of active pharmacological treatment and decreased during the subsequent placebo period (Table 2). The trend in both groups was similar; indeed at the end of the first treatment period, there was an increase of 7.1% in compliance in the CS group and 15.8% in the DS

Table 3. Physician global assessment on the patients' response to therapy (recorded on Day 180).

Judgment	CS Group		DS Group	
	N	%	N	%
Very good	42	65	8	13
Good	17	26	41	67
Fair	3	4.5	8	13
Poor	3	4.5	4	7

group. After 3 months of treatment with placebo, compliance returned to baseline values.

There were a total of 6 adverse drug events (3 in each group) considered to be possibly or probably related to treatment. In the CS group, 2 patients reported the onset of slight gastric pyrosis after 10 days of treatment and one patient reported the onset of epigastric phenomena at the beginning of the study. In the DS group, 2 patients reported the onset of epigastralgia, while one patient reported nausea after 5, 10, and 20 days of treatment. The severity of symptoms was mild in 2 cases and moderate in the other.

DISCUSSION

Due to the lack of an etiopathogenic therapy, the treatment of OA is based on a series of physico-behavioral (body weight trend, variations of physical and working activity), surgical (correction of the static–dynamic alterations of the osseous segments, when possible), medical (reequilibrium of dysmetabolic situations), physical (local heat, thermal cure), and pharmacological measures. The latter, reviewed by Lequesne[20], mostly fall into 3 categories: (1) analgesics and nonsteroidal antiinflammatory agents (NSAID); (2)

Table 4. Algofunctional Lequesne Index (hip and knee).

Pain or discomfort (0 = no pain)	
A. During nocturnal bed rest	( ) 0
Only on movement or in certain positions	( ) 1
Without movement	( ) 2
B. Duration of morning stiffness or pain after getting up	( ) 0
≤ 15 min	( ) 1
>15 min	( ) 2
C. Remaining standing for about 0.5 h	( ) 0
	( ) 1
D. Pain on walking	( ) 0
Only after walking some distance	( ) 1
Early after starting	( ) 2
E. Pain or discomfort in sitting position	( ) 0
Hip: in prolonged sitting position (2 h)	( ) 1
Knee: to get up from a sitting position without using hands	( ) 1
Maximum distance walked	
Without limits	( ) 0
More than 1 km, but limited	( ) 1
About 1 km (about 15 min)	( ) 2
From 500 to 900 m (about 7–15 min)	( ) 3
From 300 to 500 m	( ) 4
From 100 to 300 m	( ) 5
Less than 100 m	( ) 6
With one walking stick or crutch	( )+1
With two walking sticks or crutches	( )+2
Activities of daily life (0 = no difficulty, 0.5 = with little difficulty, 1= with some difficulty, 1.5 = difficult, 2 = impossible)	
Hip	
Can you put on socks by bending forward?	( ) 0 to 2
Can you pick up an object from the floor?	( ) 0 to 2
Can you go up and down a standard flight of stairs?	( ) 0 to 2
Can you get in or out of a car?	( ) 0 to 2
Knee	
Can you go up a standard flight of stairs?	( ) 0 to 2
Can you go down a standard flight of stairs?	( ) 0 to 2
Can you crouch?	( ) 0 to 2
Can you walk on an irregular floor?	( ) 0 to 2
Total score (0 to 24)	

symptomatic slow acting drugs for OA; (3) chondroprotective or truly disease modifying agents not yet available. NSAID, though they overcome the painful symptoms that are known to accompany the periodic outbreaks of acute inflammation, are not able to modify the disease itself or its evolution; moreover, the antalgic effect of these preparations — which inhibit the natural protection that pain provokes in a lesioned organ and when it is spared through spontaneous reflex, is spared in its function — could indirectly aggravate the wear and tear of the joint due to functional overloading in the phases of acute inflammation. In addition, due to their pharmacological properties, NSAID often present problems of tolerability, especially at the gastrointestinal level, and should not be used for prolonged treatment (which is typical in a chronic degenerative disease such as OA), especially in the elderly.

Good evidence is now available that symptomatic slow acting drugs are valuable therapeutic tools for OA[21,22]. At present, several data demonstrate that CS is absorbed after oral administration[23,24] and promotes the modification of the clinical picture of OA acting as a symptomatic slow acting drug[15,16,25]. The pharmacological properties and the clinical importance of the preparation seem to be confirmed by the results of our study. Indeed, diclofenac, a well known NSAID used extensively in joint pathology, showed prompt and potent analgesic/antiinflammatory efficacy during the administration period; however, when treatment was suspended, the clinical picture showed progressive regression toward the previous state, confirming that NSAID are not able to modify the natural course of the disease. On the other hand, the intake of CS was associated with relatively slow variation in the symptoms (modifications were evident from Day 30 of the treatment), later presenting a global efficacy that is comparable to that of diclofenac; however, the therapeutic effects lasted longer, even after the suspension of treatment. Symptoms tended to reappear only towards the 6th (and final) month of the observation period.

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