

***Harpagophytum procumbens* in the treatment of knee and hip osteoarthritis. Four-month results of a prospective, multicenter, double-blind trial versus diacerhein**

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Summary – Objective. To evaluate the efficacy and safety of *Harpagophytum* in the treatment of hip and knee osteoarthritis comparatively with the slow-acting drug for osteoarthritis, diacerhein. **Patients and methods.** A multicenter, randomized, double-blind, parallel-group study was conducted in 122 patients with hip and/or knee osteoarthritis. Treatment duration was four months and the primary evaluation criterion was the pain score on a visual analog scale. *Harpagophytum* 2,610 mg per day was compared with diacerhein 100 mg per day. **Results.** After four months, considerable improvements in osteoarthritis symptoms were seen in both groups, with no significant differences for pain, functional disability, or the Lequesne score. However, use of analgesic (acetaminophen-caffeine) and nonsteroidal anti-inflammatory (diclofenac) medications was significantly reduced in the *Harpagophytum* group, which also had a significantly lower rate of adverse events. **Conclusion.** In this study, *Harpagophytum* was at least as effective as a reference drug (diacerhein) in the treatment of knee or hip osteoarthritis and reduced the need for analgesic and nonsteroidal anti-inflammatory therapy. Joint Bone Spine 2000; 67 : 462-7. © 2000 Éditions scientifiques et médicales Elsevier SAS

clinical trial / diacerhein / *Harpagophytum* / hip osteoarthritis / knee osteoarthritis

Although the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of osteoarthritis has been convincingly demonstrated, their toxicity is equally well documented. Gastrointestinal side effects are particularly worrisome. The risk of side effects increases with advancing age. Furthermore, the effects of chronic or repeated use on the cartilage remain unknown [1]. These facts have placed the risk-benefit ratio of NSAIDs under scrutiny.

In patients with symptomatic degenerative joint disease, the appropriateness of NSAID therapy should be evaluated carefully [1]. The 5th ILAR/WHO Task

Force Meeting on Rheumatic Diseases stated that conventional NSAIDs should not be used in the first-line treatment of degenerative disease [2].

NSAIDs are used to provide immediate relief from pain and functional impairment. A number of newer drugs exhibit delayed but prolonged symptomatic effects that reduce the need for other drugs, including NSAIDs.

Harpagophytum procumbens has shown anti-inflammatory effects in animal models of chronic inflammation [3]. Furthermore, analgesic effects have been reported in vivo [4]. In several placebo-controlled

studies in humans, *Harpagophytum* significantly relieved low back pain [5, 6]. These data indicate that *Harpagophytum* may be beneficial in chronic joint disease.

The present double-blind study versus diacerhein was designed to evaluate the efficacy and safety of *Harpagophytum* in relieving pain, improving function, and decreasing analgesic and NSAID use in patients with hip or knee osteoarthritis.

PATIENTS AND METHODS

Patients

Patients of either sex aged 30 to 80 years were eligible if they met American College of Rheumatology criteria for femorotibial osteoarthritis and/or primary hip osteoarthritis in one or both legs and if radiographs taken during the last six months showed that the disease was Kellgren and Lawrence stage I, II or III [7]. Patients were included during a flare-up of their disease manifesting as spontaneous pain scoring 50 mm or more on a 100-mm visual analog scale (VAS) and as a Lequesne algofunctional index value of 4 or more. Exclusion criteria were secondary knee or hip osteoarthritis, severely incapacitating osteoarthritis requiring surgical treatment, serious concomitant disease, local or systemic glucocorticoid therapy within the last month, and treatment with a slow-acting drug for osteoarthritis within the last two months. No wash-out period was required for analgesics and NSAIDs.

Thirty rheumatologists recruited 122 patients, who were assigned at random to *Harpagophytum* (Harpadol®) six capsules per day or diacerhein (ART50®) two capsules per day.

Study design

The study protocol was approved by the appropriate ethics committee and the study was conducted in accordance with the Declaration of Helsinki (1964). Written informed consent was obtained from all study subjects. Randomization was performed by blocks of four patients at each study center.

The double-dummy technique was used to ensure double-blinding, as the two drugs could not be prepared as identically-appearing capsules. Each patient took two medications, one active drug and one placebo, so that the two treatments were indistinguishable from each other.

Analgesic and NSAID therapy was permitted to control clinical flares of osteoarthritis. To improve uni-

formity, this treatment was standardized as follows: an acetaminophen-caffeine combination was used first in the event of a painful flare-up, and if the response was inadequate diclofenac 50 mg was used in a daily dosage of no more than three tablets. The patients were asked to take these drugs only if they experienced clinical symptoms and to record all doses in a diary. Acetaminophen-caffeine and diclofenac use was recorded by the investigator in the case report form.

After an inclusion visit on day 0, the efficacy, safety, and beneficial therapeutic effects of the treatment were evaluated on days 30, 60, and 120 using the criteria outlined below.

Efficacy criteria

The primary efficacy criterion was the severity of spontaneous pain as assessed using a Huskisson VAS [8].

Secondary efficacy criteria were the daily doses of diclofenac and acetaminophen-caffeine, functional disability assessed on a VAS, the value of the Lequesne algofunctional index for hip or knee osteoarthritis [9], and overall assessments performed by the patient and the investigator using a five-point verbal scale.

Safety criteria

Adverse events were collected at each visit. For each event, the nature, duration, severity, outcome, and causal link with the study treatment as evaluated by the investigator were recorded in the case report form. The number of patients with at least one adverse event and the number of patients withdrawn from the study because of adverse events were determined. Overall safety assessments by the patient and investigator were recorded.

Statistical methods

This was a one-sided equivalence and noninferiority trial of *Harpagophytum* versus diacerhein, with spontaneous pain on a 100-mm VAS as the primary criterion. A one-sided equivalence test was used with the α risk set at 0.05. No major deviations from the protocol were recorded, and consequently all the study patients were included in the statistical analysis. Per protocol and intention-to-treat analyses were done. In the intention-to-treat analysis, the last observation carried forward method was used to replace missing data. All the study patients who came to the D30 visit were included in the intention-to-treat analysis, whereas attendance at the D120 visit was required for inclusion in the per protocol analysis.

Table I. Reasons for study withdrawals.

	nmtm (n = 62)		Diacerhein (n = 60)*	
	N	%	N	%
Lost to follow-up	0	0%	4	7%
Adverse events	8	13%	14	23%
Inefficacy	2	3%	1	2%
Protocol violation	1	2%	1	2%
Other	1	2%	2	3%

*In the diacerhein group, several patients had more than one reason for withdrawal.

The predefined equivalence criterion was a value smaller than 10 mm for the upper limit of the 90% confidence interval of the pain score difference between the two treatment groups.

Sample size calculation

Assuming that a true difference between the two treatments of zero with a Δ of 10 mm, a one-sided equivalence test with α set at 0.05, a β risk set at 0.10, and a standard deviation of 18 mm, the required sample size was 56 patients per group.

RESULTS

Overall 122 patients were randomized and 92 patients completed the trial in accordance with the protocol. Corresponding figures were 62 and 50 in the *Harpagophytum* group and 60 and 42 in the diacerhein group. *Table I* shows the reasons for study withdrawals.

Demographics

No statistically significant differences were found between the two treatment groups for demographic parameters, disease duration, disease severity, disease distribution, or radiological stage (*table II*).

Evaluation criteria at baseline

The spontaneous pain score was 63.6 mm in the *Harpagophytum* group and 61.6 mm in the diacerhein group ($P = 0.37$). The Lequesne algofunctional score (which is based on pain, walking distance, and impact on daily activities) was 10.25 in the *Harpagophytum* group and 9.96 in the diacerhein group ($P = 0.60$). Thus, no statistically significant differences were found at baseline between evaluation criteria in the two treatment groups (*table III*).

Table II. Demographic features in the study population.

	Harpagophytum	Diacerhein	P-value
N	62	60	
Age	62.25	61.08	$P = 0.52^*$
Sex (M/F) (N)	20/42	25/35	$P = 0.35^{**}$
Weight (kg)	72.9	76.35	$P = 0.16^*$
Height (cm)	162.9	165.6	$P = 0.09^*$
Joint involved:			
knee	44	44	$P = 0.58^{**}$
hip	18	16	
Radiological stage:			
I	10	8	
II	27	34	$P = 0.39^{**}$
III	24	18	
Osteoarthritis duration (years)	5.49	5.47	$P = 0.98^*$

* Analysis of variance, ** Fisher's test.

Table III. Evaluation criteria at baseline (mean \pm standard deviation).

	nmtm	Diacerhein	ANOVA
Pain score on D0 (mm)	63.6 \pm 13.2	61.6 \pm 11.1	$P = 0.37$
Lequesne's algofunctional index on D0	10.25 \pm 3.72	9.96 \pm 3.01	$P = 0.60$
Functional disability on D0 (mm)	59.0 \pm 18.8	58.6 \pm 16.9	$P = 0.88$

The protocol did not include a comparison of NSAID and analgesic use before study inclusion. However, it was important to check that the two groups were comparable in this respect. Consequently, we determined the numbers of tablets of diclofenac and acetaminophen-caffeine used during the first three study days, i.e., before the study treatments had had time to act. No significant differences were found: mean diclofenac use was 1.08 and 1.18 tablets in the *Harpagophytum* and diacerhein groups, respectively; corresponding numbers for acetaminophen-caffeine were 1.63 and 1.66.

Efficacy data

Primary efficacy criterion: pain scale score

In the *Harpagophytum* group, the pain score decreased steadily throughout the trial (*figure 1*). The decrease was apparent as early as day 30. A similar pattern was seen in the diacerhein group with, however, a somewhat smaller decrease on day 120. The equivalence test

Table IV. Equivalence tests based on confidence intervals of between-group differences (VAS pain score).

Variable	Mean (crude or adjusted) difference in baseline		Between-group difference (H-D) ¹	90% confidence interval of the difference (H-D)	Hypothesis: Harpagophytum is at least as good as diacerhein
	Harpagophytum	Diacerhein			
Pain score on D120	-30.6 ± 3.3	-25.5 ± 3.6	-5.1	-13.1; 3.0	Accepted
LO ² for the pain score	-28.8 ± 3.2	-22.1 ± 3.2	-6.7	-14.2; 0.9	Accepted

¹A negative difference is in favor of *Harpagophytum*. ²"as good as" defined as not inferior by more than 10 mm; last observation made under treatment.

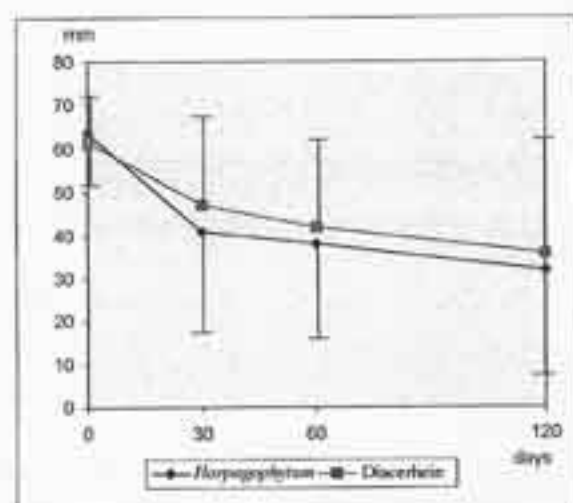


Figure 1. Self-evaluation of pain severity using a Huskisson visual analog scale (0 to 100 mm).

was significant ($P = 0.001$), demonstrating that *Harpagophytum* was at least as effective as diacerhein. Table IV reports the results of equivalence tests performed using pain score values on day 120 in the per protocol population and pain scores at the last visit under treatment in the intention-to-treat population. In both analyses, the upper limit of the 90% confidence interval for the between-group difference was under 10 mm, confirming that *Harpagophytum* was at least as effective as diacerhein.

Secondary criteria

Lequesne algofunctional index for knee and hip osteoarthritis

The Lequesne algofunctional index value decreased from one visit to the next (figure 2), following a similar pattern in the two treatment groups. At study comple-

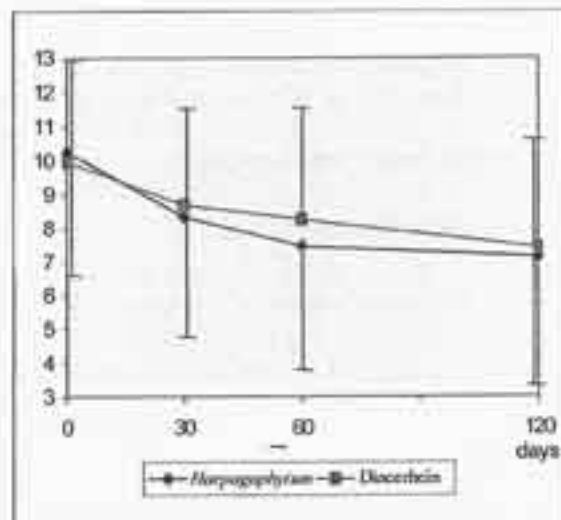


Figure 2. Lequesne's algofunctional index (0 to 24).

tion (day 120), the difference between the two groups was not statistically significant ($P = 0.71$; analysis of variance).

Use of diclofenac and acetaminophen-caffeine

Patients in the *Harpagophytum* group used significantly fewer diclofenac tablets than the patients in the diacerhein group (table V). This difference was apparent as early as day 30 and was statistically significant on days 60 and 120. By day 120, mean cumulative diclofenac use was 20.9 tablets in the *Harpagophytum* group versus 55.5 tablets in the diacerhein group ($P = 0.002$; analysis of variance).

Similar results were found for the use of acetaminophen-caffeine (table V). By day 120, the mean cumulative number of tablets was significantly smaller in the *Harpagophytum* group (39.7) than in the diacerhein group (59.5) ($P = 0.002$; analysis of variance).

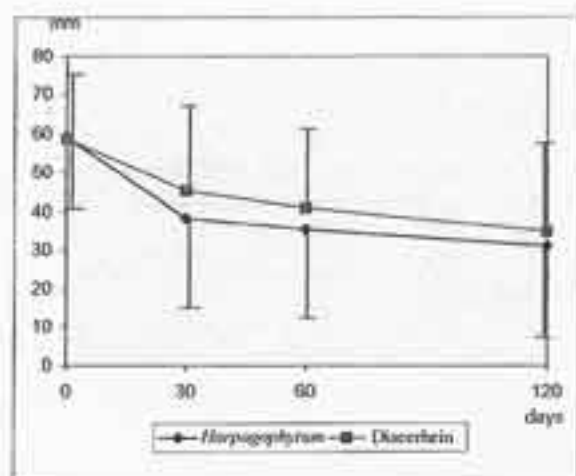


Figure 3. Self-evaluation of functional impairment using a Huskisson visual analog scale (0 to 100 mm).

Functional impairment

Functional impairment improved steadily in both groups (figure 3). At study completion (day 120), no

Table V. Cumulative number of tablets of analgesic (acetaminophen-caffeine) and NSAID (diclofenac) used in each group.

	D30	D60	D120
<i>Harpagophytum</i>			
NSAID	7.17	11.52*	20.9*
Analgesic	11.35	21.08*	39.72*
<i>Diacerhein</i>			
NSAID	11.78	28.5	55.15
Analgesic	12.96	32.46	59.55

* $P < 0.05$ between the two groups.

statistically significant difference was found ($P = 0.43$; analysis of variance).

Overall assessments

Efficacy was considered good or excellent by the investigators in 65.3% of the *Harpagophytum* patients and 60% of the diacerhein patients. The assessments by the patients showed similar results, with good or excellent efficacy in 63.5% of the *Harpagophytum* patients and 64.5% of the diacerhein patients.

Safety

A significantly smaller number of *Harpagophytum* patients experienced one or more adverse events, as compared to the diacerhein patients ($P = 0.042$, χ^2 test).

Causality was assessed by the investigator as probable, possible, or improbable. The number of patients

Table VI. Gastrointestinal adverse events.

	<i>Harpagophytum</i>	<i>Diacerhein</i>
Diarrhea	5 (8.1%)	16 (26.7%)
Abdominal pain	2 (3.2%)	5 (8.3%)
Vomiting	2 (3.2%)	2 (3.3%)
Constipation	1 (1.6%)	—
Flatulence	3 (4.8%)	—
Dyspepsia	3 (4.8%)	3 (4.8%)

with at least one adverse event considered possibly or probably related to the study treatment was ten in the *Harpagophytum* group and 21 in the diacerhein group ($P = 0.017$, χ^2 test). Most adverse events were gastrointestinal complaints; their nature and frequency are reported in table VI. Diarrhea was the most common adverse event, with 26% of cases in the diacerhein group and 8.1% in the *Harpagophytum* group.

DISCUSSION

NSAIDs are a time-honored treatment for the pain caused by osteoarthritis. Their efficacy has been demonstrated in many therapeutic trials. Their prompt pain-relieving effect is valuable in flare-ups of osteoarthritis symptoms. However, their effects on the cartilage, or absence thereof, remain unknown.

Slow-acting drugs for osteoarthritis (SADOAs) are newer agents whose effects are both delayed and prolonged. They have been found effective in relieving the symptoms of osteoarthritis. However, there is no proof that they have structural effects. SADOAs are useful as maintenance therapy in patients with chronic or recurrent symptoms that fail to respond adequately to non-pharmaceutical measures. Their main advantage is that they reduce the need for analgesics or NSAIDs, thus decreasing the risk of side effects related to these compounds.

The objective of the current study was to determine whether *Harpagophytum* given for four months is effective in the treatment of osteoarthritis. No placebo arm was used because patients often decline participation in a study involving a 50% likelihood of receiving a pla-

cebo, particularly when the treatment is long-term (four months in the present study). *Harpagophytum* was compared to diacerhein, a SADOA whose efficacy has been convincingly demonstrated in studies versus a placebo or NSAID [10, 11].

The magnitude of the placebo effect in osteoarthritis has been evaluated recently [12] in a review of six controlled studies of symptomatic SADOA including 457 patients in all. The mean decrease in the VAS pain score was 10 to 16 mm in the placebo arms [12]. This is far less than the 30.6-mm decrease seen with *Harpagophytum* in our study.

We found that *Harpagophytum* and diacerhein were equivalent in terms of pain relief, which was the primary efficacy criterion in our study. Equivalence was also demonstrated for the Lequesne algofunctional index and the functional disability VAS score. In addition, patients on *Harpagophytum* required significantly smaller amounts of analgesic and NSAID tablets than patients on diacerhein.

The number of adverse events was significantly smaller in the *Harpagophytum* group. Patients in the diacerhein group were more likely to be withdrawn from the study because of adverse events.

The results of this trial confirm that *Harpagophytum* is effective on the main clinical parameters used to assess osteoarthritis (pain, functional impairment and Lequesne score). They highlight the good safety profile of *Harpagophytum*, a valuable feature in drugs used for long-term therapy.

CONCLUSION

This double-blind controlled study versus a reference drug conducted in accordance with Good Clinical Practice guidelines demonstrates that *Harpagophytum* is as least as effective as a reference drug (diacerhein) in the treatment of hip or knee osteoarthritis and significantly reduces the need for analgesic and NSAID agents. Further studies are needed to determine the

kinetics of the effects of *Harpagophytum* and the place of this agent in the therapeutic armamentarium.

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