RESULTS

During the one week run-in period, 5 of the 200 subjects considered eligible for the study dropped out and the other 2 subjects were withdrawn due to hypersensitivity to paracetamol and spontaneous relief of pain. The remaining 193 subjects constituted the study population and were randomized into 4 parallel groups: 47 for placebo group, 49 for diclofenac group, 48 for EA group and 49 for combined group (Figure 2). The four treatment groups were not significantly different in base-line characteristics (Table 2.1) and base-line data (Table 2.2) for the major outcome assessments, e.g., sex, age, weight, height, duration of disease, localisation of OA, amount of paracetamol consumption, VAS, WOMAC, Lequesne's functional index and 50 feet-walk time. There were no differences in mean serum concentrations of cartilage markers evaluated at the end of run-in peroid among the four groups (Table 2.3). The radiographic findings at entry (Table 3) were not different among the four groups. Previous OA treatments of the patients and their therapeutic outcome are shown in Table 4 and 5, respectively. Most of the patients had been treated by at least one treatment procedure before entry into this study. The most common procedures were oral medications (e.g., paracetamol, NSAIDs, muscle relaxants, etc.) followed by topical medications (e.g., various types of balm and gel) and intramuscular injection of NSAIDs, respectively. Intraarticular injection as well as physical therapy and other traditional treatments (e.g., oral or topical herbal medicine, traditional massage, acupuncture, etc.) were less common. Most patients experienced temporary improvement from previous treatments. The concomitant treatments of coexisting disorders among the patients are shown in Table 6. More than 60% of the patients used no concomitant treatments during this study. The most common drug therapy used in concomitant treatment was cardiovascular drugs (e.g., antihypertensives, antianginals, etc.). However, the proportions of patients used concomitant treatments among the four groups were not significantly different.

Of the 193 study patients, 186 (96.37%) completed the study. The remaining 7 patients were withdrawn from the trial. The reasons for withdrawal and time of withdrawal from the trial are presented in Table 7. Two patients in the placebo group

were withdrawn due to flare of pain with joint swelling, while 3 patients in the combined group were withdrawn due to GI side effects (such as dyspepsia, burning sensation at epigastrium or abdominal pain). Only 1 patients in the EA group was withdrawn due to flare of pain with joint swelling, while another was withdrawn due to the reason not related to EA treatment, i.e., flare of pain from accidental fall. No patient in the diclofenac group was withdrawn. Since there were few patients withdrawn from the trial, the results therefore were not substantially affected whether analysis performed by an intention to treat analysis or an analysis on available completers. Thus, the remaining data showed the findings in only 186 avialable completers (Figure 2).

During four weeks of treatment, changes in body weight compared to the base-line values did not significantly differ among the four groups (one-way ANOVA calculated each week, data not presented). The rates of compliance with medications (placebo or diclofenac) in the placebo, diclofenac, EA and combined groups were 93.62, 96.33, 93.58 and 94.59%, respectively, whereas the rates of compliance with acupuncture (placebo or EA) in the four groups were 98.15, 97.96, 97.83 and 98.37%, respectively. Thus, the rates of compliance with both medications and acupuncture were comparable among the four groups.

The average amount of paracetamol tablets taken/week (Figure 3) at any time-points in each group (except at week 3 in placebo and week 1 in EA group) significantly decreased when compared to their own base-line values. During week 4, the greatest reduction in average amount of paracetamol consumption from baseline was found in EA group (-36.45%) followed by combined (-26.91%), placebo (-23.55%), and diclofenac groups (-23.38%), respectively. However, the mean changes in paracetamol consumption among the four groups at each time-point were not statistically significant (Table 8).

The median 100 mm VAS at any time-points in all groups decreased significantly when compared to their own base-line values, as did WOMAC pain index, stiffness index (except at week 1 in placebo group), disability index, total score and Lequense's functional index (Figure 4-9 and Table 9-14). At week 4, the reduction in median 100 mm VAS from baseline was greatest in EA group followed by combined, diclofenac and placebo groups, respectively (decreased by 81.38, 67.92, 63.64 and 36.84%, respectively). The differences in median values of 100 mm VAS among the four

groups were not statistically significant at the first week, but there were significant differences between placebo versus EA groups at week 2-4, placebo versus combined groups and EA versus diclofenac groups at week 4 (Figure 4 and Table 9).

At week 4, the reduction in median WOMAC pain index from baseline (Figure 5 and Table 10) was greatest in EA and combined groups (-60%) followed by diclofenac (-50%) and placebo groups (-40%), respectively. The reduction in median WOMAC stiffness index from baseline (Figure 6 and Table 11) was greatest in EA group (-60%) followed by combined as well as diclofenac (-50%), and placebo groups (-25%), respectively. In contrast, the reductions in the median values of WOMAC disability index and total score at week 4 compared to the base-line values (Figure 7-8 and Table 12-13) were greatest in EA group followed by combined, diclofenac and placebo groups, respectively (disability index decreased by 60.24, 53.43, 39.40 and 32.36%, respectively and total score decreased by 57.01, 53.92, 41.30 and 36%, respectively). However, there were only significant differences in the median values of WOMAC pain index between placebo versus combined groups and WOMAC stiffness index between placebo versus EA groups at the fourth week.

At week 4, the reduction in median Lequense's functional index from baseline was greatest in EA group (-51.72%) followed by combined as well as diclofenac (-39.28%), and placebo groups (-27.59%), respectively. Nonetheless, the differences in the Lequense's functional index among the four groups at each time-points were not statistically significant (Figure 9 and Table 14).

The mean 50 feet-walk time at any time-points in all groups significantly decreased when compared to their own base-line values (Figure 10). At the end of the study, the greatest reduction in mean 50 feet-walk time from baseline was found in EA group (-18.17%) followed by combined (-18.03%), diclofenac (-15.72%) and placebo groups (-12.42%), respectively. However, the magnitude of changes compared to the base-line values at each time-point did not significantly differ among the four groups (Table 15).

The orthopedist's and patient's overall opinions toward the therapeutic outcome are shown in Table 16-19. The number of patients with overall opinions of "much better" increased every week. At week 3 and 4 (Table 18-19), the number of patients with orthopedist's and patient's overall opinions of "much better" were greatest in EA group

followed by diclofenac, combined and placebo groups, respectively. However, there were only statistical differences among the four groups in orthopedist's overall opinion at the last two weeks.

The number of the patients considered to be responders in all groups increased every week (Table 20). At the end of the study, the percentage of responders was greatest in EA group (58.70%) followed by combined (50.00%), diclofenac (36.73%) and placebo groups (28.89%), respectively. There were significant differences in the number of responders among the four groups at week 4, but not at the previous 3 weeks.

The percentage of patients experienced adverse events during the study are shown in Table 21. The percentage with gastrointestinal and central nervous system symptoms, rash, edema, and hypertension did not differ among the four groups, whereas those with local contrusions were significantly high in EA and combined groups (aproximately 45%). However, the contrusions were usually self-limited within 5-7 days. When the responders at week 4 in each group were followed up to 2 months, the proportions of remaining responders were not significantly different among the four groups (Table 22).

In a partial cross-over section of this study, 32 patients considered to be non-responders at the end of week 4 in placebo (17 patients) or diclofenac groups (15 patients) were subsequently switched to EA treatment for 4 weeks (EA phase, week 5-8). During EA phase, 3 patients in each group dropped out and 2 patients in diclofenac group were withdrawn due to inffectiveness. Thus, there were 14 and 10 completers in placebo and diclofenac groups, respectively. Using within group analysis on avialable completers, the mean body weight at week 0 and week 8 in each group did not differ significantly (paired t-test, data not presented). At week 4, there was no significant reduction in average amount of paracetamol tablets taken/week in both groups (Figure 11), whereas the median values of VAS, WOMAC score and Lequense 's functional index in both groups differed significantly from their own base-line values (Figure 12-14). At week 8, the further and significant reductions from baselines in these median values as well as the average amount of paracetamol consumption were also demonstrated in both groups (Figure 11-14). In addition, the significant reductions in all values from those of week 4 were also found in placebo group,

whereas diclofenac group showed only significant reductions in median values of Lequense's functional index and WOMAC score. Five patients in each group previously not responded to either treatment were considered to be responders at the end of EA phase.

The fluctuation in mean serum concentrations of HA as well as CS 3-B-3(+) and W-F-6 epitopes in all groups (except for those of CS W-F-6 in placebo group) were observed during the study time. However, these values did not change significantly from their own base-line values (Figure 15-17). In addition, the mean changes in serum concentrations of these cartilage markers at each time-point did not differ among the four groups (Table 23-25).

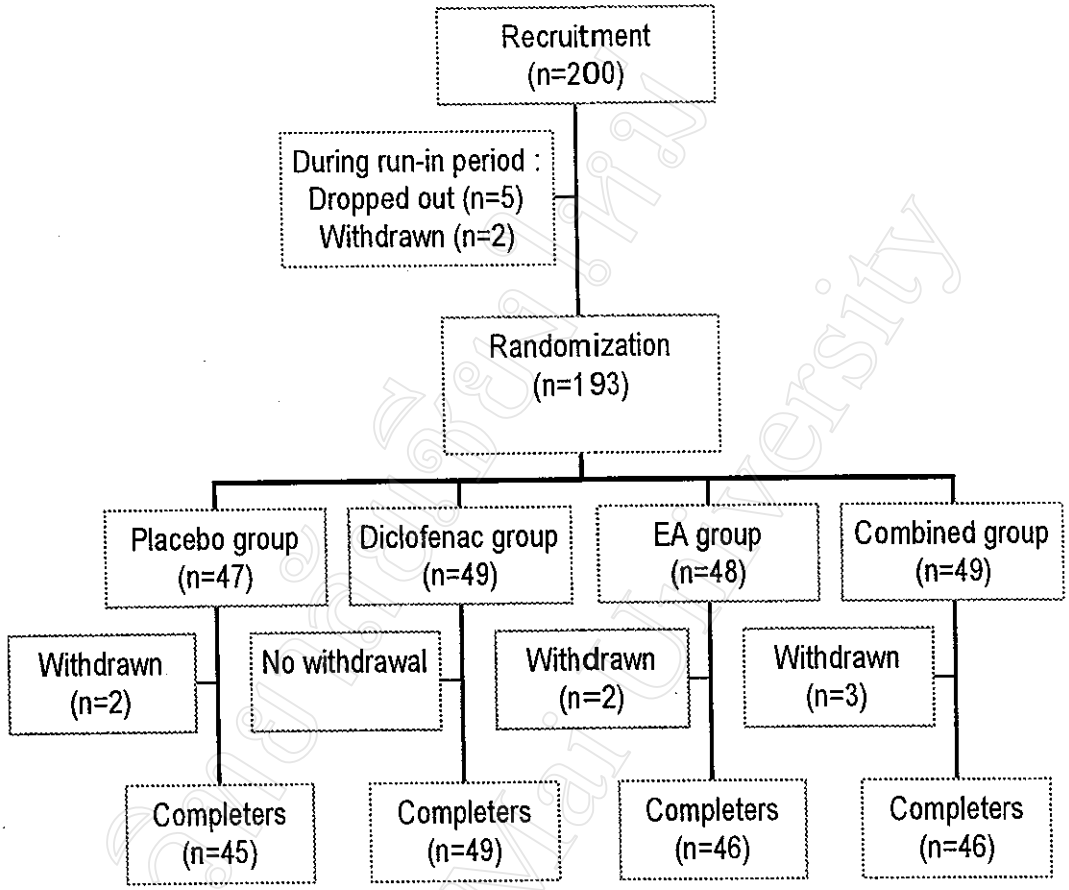

Figure 2. Flow chart of randomization as well as dropout and withdrawal in the study.

Table 2.1. Demographic data of participants evaluated at the end of run-in period (week 0).

Characteristic	Treatment groups				*p* value
	Placebo	Diclofenac	EA	Combined	
n (M:F)	47 (12:35)	49 (11:38)	48 (10:38)	49 (10:39)	0.93[c]
Age (yr)*	62.70	62.14	65.10	61.84	0.16[a]
	(7.22)	(7.53)	(3.40)	(8.95)	
Body weight (kg)*	60.65	57.65	59.89	59.92	0.49[a]
	(10.24)	(10.64)	(9.74)	(9.66)	
Height (cm)*	153.94	151.94	152.19	153.32	0.54[a]
	(6.45)	(10.71)	(5.89)	(6.73)	
Duration of OA (yr)*	4.98	3.94	6.09	4.53	0.05[a]
	(3.32)	(2.83)	(4.96)	(3.86)	
Localisation of OA					0.71[c]
Right knee	2	2	1	3	
Left knee	3	6	4	5	
Both knees	42	41	43	41	

*Data represent mean (SD).

Statistic analysis: a = one-way ANOVA, c = chi-square test.

Table 2.2. Base-line data for the major outcome assessments of participants evaluated at the end of run-in period (week 0).

Characteristic	Treatment groups				*p* value
	Placebo	Diclofenac	EA	Combined	
Paracetamol tablets taken/week*	22.06 (13.75)	18.94 (14.68)	21.40 (14.97)	19.04 (14.87)	0.63[a]
100 mm VAS**	57 (12-100)	66 (20-100)	61.75 (20-100)	53 (5-100)	0.21[k]
WOMAC score**	52 (13-87)	46 (18-96)	53.5 (14-92)	51 (19-95)	0.96[k]
Lequesne's index**	14.5 (6-19.5)	14 (7-21)	14.5 (6.5-20)	14 (7-20)	0.93[k]
50 feet-walk time* (sec)	22.04 (4.81)	22.36 (6.00)	24.54 (8.14)	22.77 (5.13)	0.21[a]

* Data represent mean (SD).

**Data represent median (range).

Statistic analysis: a = one-way ANOVA, k = Kruskal Wallis test.

Table 2.3. Mean serum concentrations of cartilage markers of participants evaluated at the end of run-in period (week 0)*.

Characteristic	Treatment groups				*p* value**
	Placebo	Diclofenac	EA	Combined	
Serum HA concentration (ng/ml)	219.18 (300.90)	149.74 (101.04)	165.66 (149.32)	188.45 (244.30)	0.41
Serum 3-B-3(+) concentration (ng/ml)	144.06 (187.01)	108.34 (108.42)	195.13 (484.89)	131.21 (234.61)	0.51
Serum W-F-6 concentration (μg/ml)	4.45 (4.78)	14.09 (43.98)	6.11 (9.35)	6.35 (13.76)	0.19

* Data represent mean (SD).

**One-way ANOVA.

Table 3. The radiographic findings at entry into the study*.

Radiographic findings	Treatment groups				*p* value
	Placebo (89 knees)	Diclofenac (90 knees)	EA (91 knees)	Combined (90 knees)	
Kellgren and Lawrence X-ray grade [77]					
Grade 1	4	1	3	5	0.40[f]
Grade 2	4	6	5	7	0.84[f]
Grade 3	19	15	25	23	0.31[c]
Grade 4	62	68	58	55	0.16[c]
Knee compartment with most severe changes of OA					
Medial tibiofemoral	63	77	69	64	0.73[c]
Lateral tibiofemoral	12	5	13	11	0.24[c]
Patellofemoral	14	8	9	15	0.28[c]

*Data represent number of patients.

Statistic analysis: c = chi-square test, f = Fisher's exact test.

Table 4. Percentage of the patients received previous OA treatments prior to this study*.

	Treatment groups			
Treatment procedures	Placebo (n=47)	Diclofenac (n=49)	EA (n=48)	Combined (n=49)
Oral medication	93.62	93.88	100.00	93.88
Topical medication	85.11	89.80	89.58	87.76
Intramuscular injection of NSAIDs	72.34	67.35	75.00	71.43
Intraartricular injection/aspiration	29.79	40.82	33.33	40.82
Oral herbal medication	40.43	30.61	45.83	26.53
Topical herbal medication	29.79	24.49	37.50	16.33
Physical therapy	17.02	18.37	22.92	26.53
Traditional massage	21.28	32.65	43.75	22.45
Acupuncture	2.13	4.08	2.08	2.04
Miscellaneous	2.13	0	0	0
No treatment	0	4.08	0	0

*More than one treatment procedures might be used.

Table 5. Percentage of the patients self-rated the outcome of previous OA treatment.

	Treatment groups			
	Placebo	Diclofenac	EA	Combined
Therapeutic outcome	(n=47)	(n=49)	(n=48)	(n=49)
Worse	0	0	2.08	2.04
Same	4.26	4.08	12.50	10.20
Temporary improvement	95.74	87.76	81.25	87.76
Much better	0	4.08	4.17	0
No treatment	0	4.08	0	0

Table 6. Percentage of the patients used concomitant drug therapy during the study*.

	Treatment groups				
	Placebo (n=47)	Diclofenac (n=49)	EA (n=48)	Combined (n=49)	*p* value
No concomitant drug therapy	76.60	79.59	58.33	73.47	0.09[c]
Cardiovascular drugs	12.77	12.24	33.33	18.37	0.07[f]
Anti-diabetics	4.26	4.08	10.42	2.04	0.36[f]
Lipid lowering drugs	0	4.08	4.17	0	0.31[f]
Thyroid/ Anti-thyroid drugs	4.26	0	4.17	2.04	0.46[f]
Vitamins/ Minerals	4.26	4.08	4.17	2.04	0.92[f]
Miscellaneous	0	0	0	2.04	1.00[f]

*More than one concomitant drug therapy might be used.

Statistic analysis: c = chi-square test, f = Fisher's exact test.

Table 7. Reasons for withdrawal and time of withdrawal (in parentheses).

Reason	Number of patients withdrawn from the study in each group			
	Placebo (n=47)	Diclofenac (n=49)	EA (n=48)	Combined (n=49)
Lack of efficacy	2 (visit #8,12)	0	1 (visit #10)	0
GI side effects	0	0	0	3 (visit #4, 4, 8)
Accidental fall	0	0	1 (visit #7)	0
Total	2	0	2	3

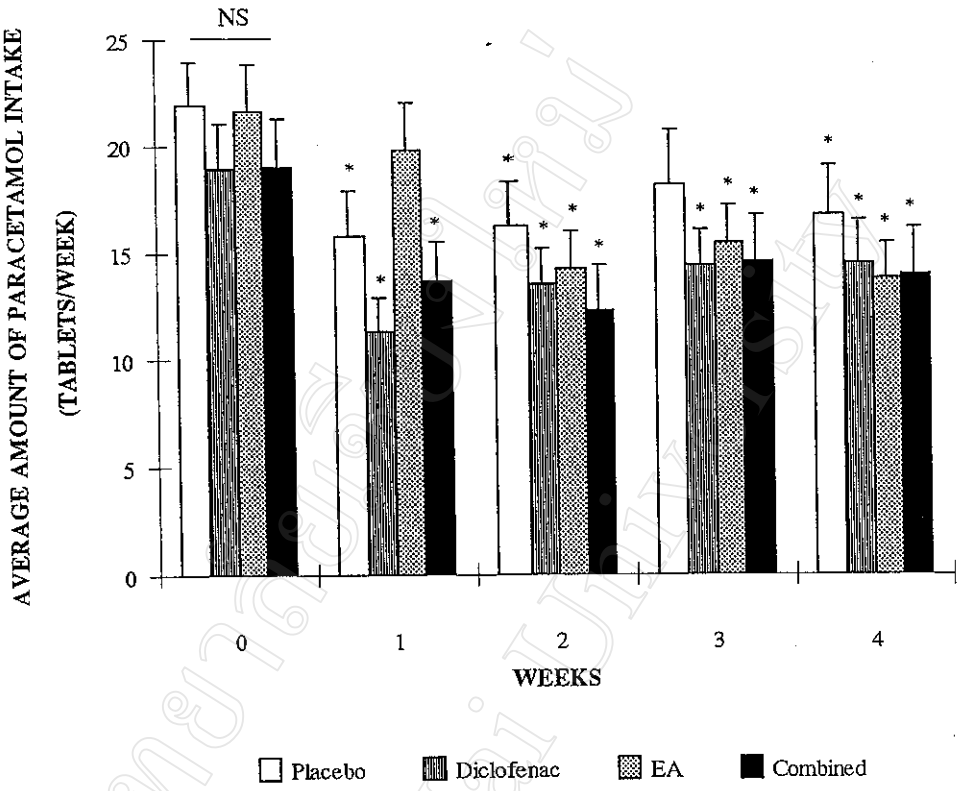

Figure 3. Average amount of paracetamol intake in each treatment group during run-in period (week 0) and during treatment. Data represent mean ± SEM. *= $p<0.05$ within group (paired t-test). NS = no significance among groups (one-way ANOVA).

Table 8. Changes in paracetamol consumption compared to the base-line values*.

Treatment groups	Paracetamol consumption at week 0 (tablets/week)	Changes in paracetamol consumption (tablets)			
		Week 0-1	Week 0-2	Week 0-3	Week 0-4
Placebo (n=45)	21.89 (13.61)	-6.13 (13.05)	-5.64 (13.99)	-3.71 (14.92)	-5.16 (15.66)
Diclofenac (n=49)	18.94 (14.68)	-7.65 (11.93)	-5.43 (12.26)	-4.57 (13.91)	-4.43 (13.32)
EA (n=46)	21.65 (15.17)	-1.80 (12.99)	-7.43 (12.98)	-6.17 (14.39)	-7.89 (14.15)
Combined (n=46)	19.07 (14.97)	-5.39 (12.18)	-6.78 (12.86)	-4.50 (14.03)	-5.13 (14.00)
p value**	0.64	0.14	0.86	0.87	0.66

* Data represent mean (SD).

** One-way ANOVA among the four groups.

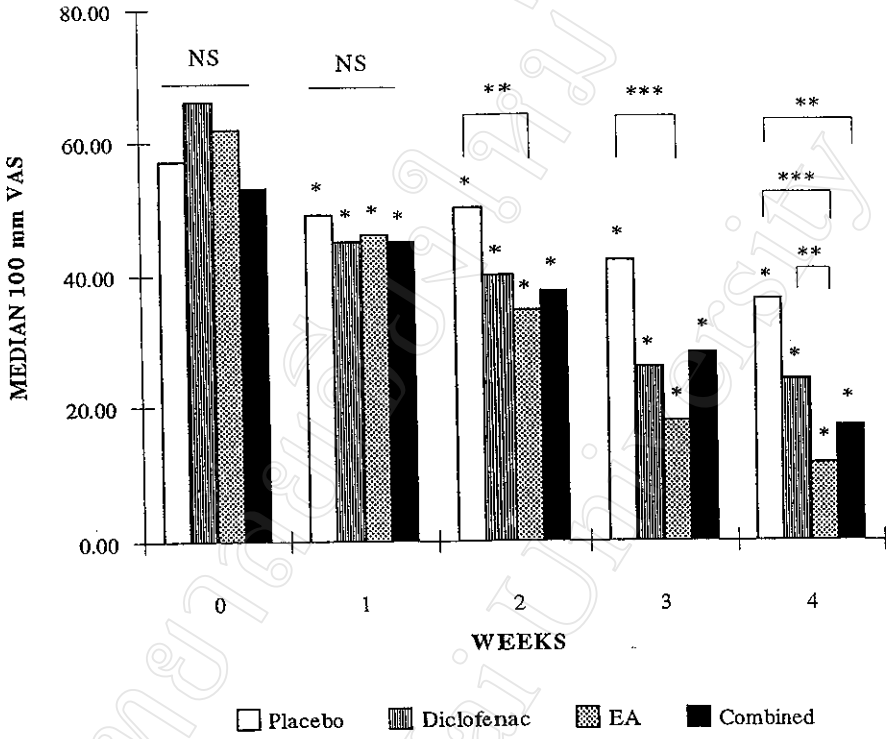

Figure 4. Median 100 mm VAS in each treatment group evaluated at the end of run-in period (week 0) and during treatment. *= $p<0.05$ within group (Wilcoxon's match paired test). NS = no significance among groups (Kruskal Wallis test). **= $p<0.05$, ***= $p<0.001$ between groups (Kruskall Wallis test and Dunn's multiple comparison).

Table 9. Median 100 mm VAS in each treatment group evaluated at the end of run-in period (week 0) and during treatment*.

Treatment groups	Time of study (weeks)				
	0	1	2	3	4
Placebo (n=45)	57 (12-100)	49† (8-100)	50† (0-100)	42† (0-100)	36† (0-100)
Diclofenac (n=49)	66 (20-100)	45† (0-100)	40† (0-100)	26† (0-100)	24† (0-100)
EA (n=46)	61.75 (20-100)	46† (3-99)	34† (0-85)	18† (0-77)	11† (0-55.5)
Combined (n=46)	53 (5-100)	45† (2-93)	37.5† (3-87)	28† (0-90)	17† (0-88)
p value**	0.39	0.24	<0.01	<0.01	<0.01

* Data represent median (range)

† $p<0.05$ within group (Wilcoxon's match paired test).

** Kruskal Wallis test among the four groups.

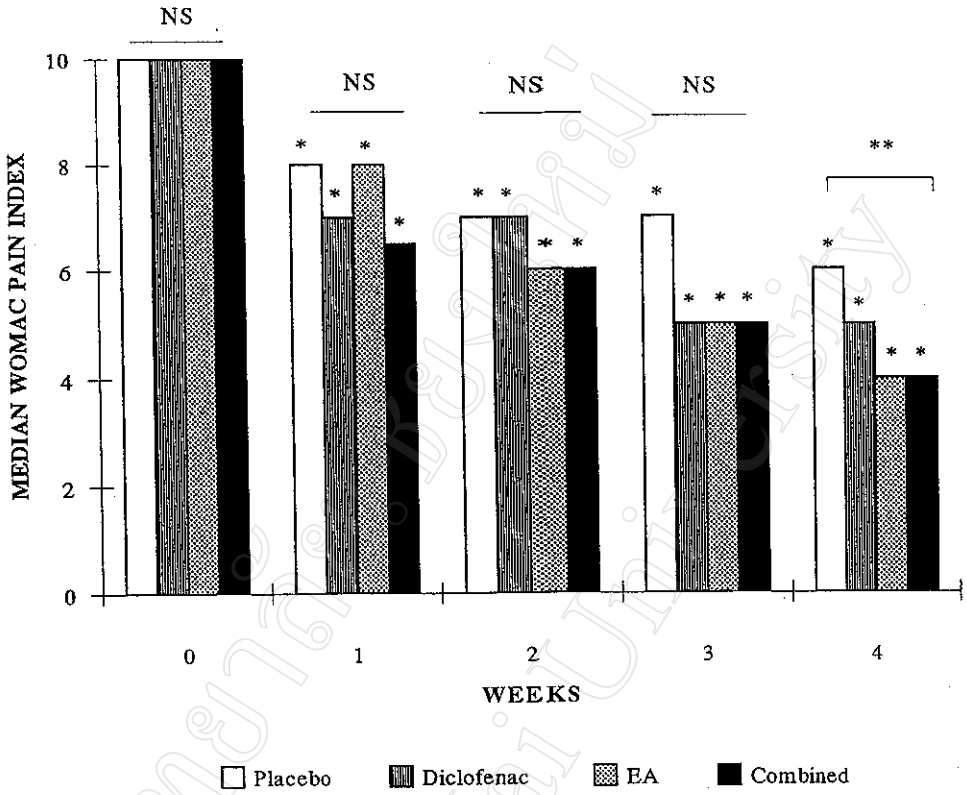

Figure 5. Median WOMAC pain index in each treatment group evaluated at the end of run-in period (week 0) and during treatment. *= $p<0.05$ within group (Wilcoxon's match paired test). NS = no significance among groups (Kruskal Wallis test). **= $p<0.05$ between two groups (Kruskal Wallis test and Dunn's multiple comparison).

Table 10. Median WOMAC pain index in each treatment group evaluated at the end of run-in period (week 0) and during treatment*.

Treatment groups	Time of study (weeks)				
	0	1	2	3	4
Placebo (n=45)	10 (0-20)	8† (0-18)	7† (0-20)	7† (0-16)	6† (0-16)
Diclofenac (n=49)	10 (2-20)	7† (0-18)	7† (1-14)	5† (0-14)	5† (0-14)
EA (n=46)	10 (3-19)	8† (1-19)	6† (0-16)	5† (0-15)	4† (0-14)
Combined (n=46)	10 (4-19)	6.5† (2-18)	6† (0-20)	5† (1-16)	4† (0-16)
p value**	0.86	0.40	0.29	0.32	0.01

* Data represent median (range).

† $p<0.05$ within group (Wilcoxon's match paired test).

** Kruskal Wallis test among the four groups.

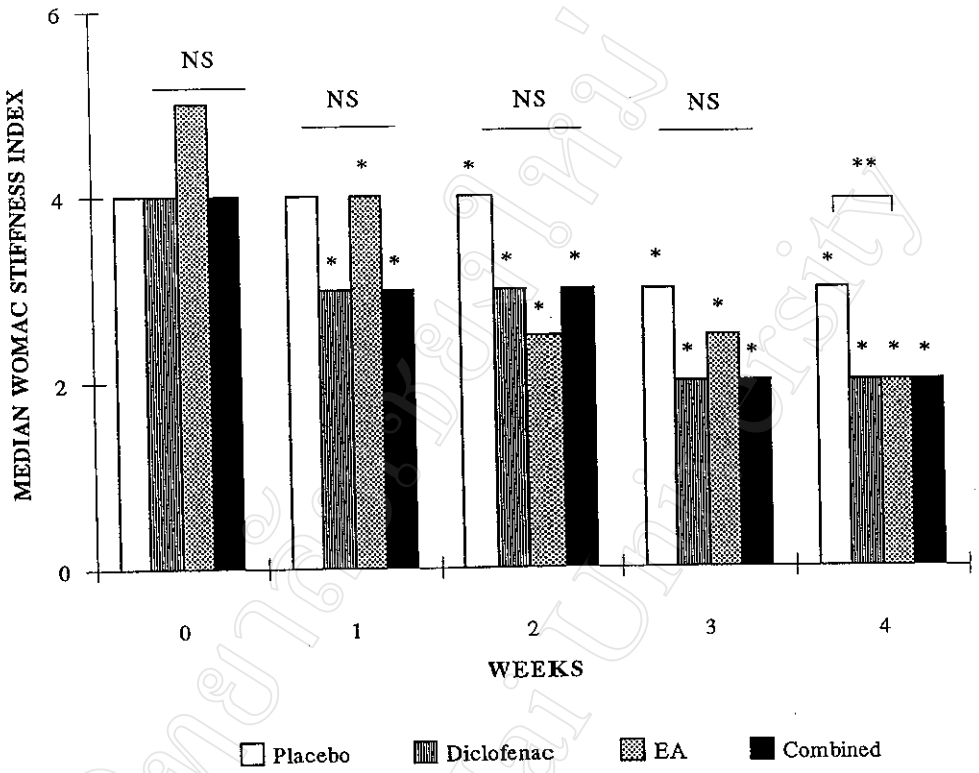

Figure 6. Median WOMAC stiffness index in each treatment group evaluated at the end of run-in period (week 0) and during treatment. *= $p<0.05$ within group (Wilcoxon's match paired test). NS = no significance among groups (Kruskal Wallis test). **= $p<0.05$ between two groups (Kruskal Wallis test and Dunn's multiple comparison).

Table 11. Median WOMAC stiffness index in each treatment group evaluated at the end of run-in period (week 0) and during treatment*.

Treatment groups	Time of study (weeks)				
	0	1	2	3	4
Placebo (n=45)	4 (1-8)	4 (0-8)	4† (0-8)	3† (0-8)	3† (0-8)
Diclofenac (n=49)	4 (1-8)	3† (0-8)	3† (0-7)	2† (0-6)	2† (0-6)
EA (n=46)	5 (0-8)	4† (0-8)	2.5† (0-8)	2.5† (0-6)	2† (0-6)
Combined (n=46)	4 (1-8)	3† (0-8)	3† (0-8)	2† (0-8)	2† (0-8)
p value**	0.65	0.10	0.50	0.43	0.03

* Data represent median (range).

† $p<0.05$ within group (Wilcoxon's match paired test).

** Kruskall Wallis test among the four groups.

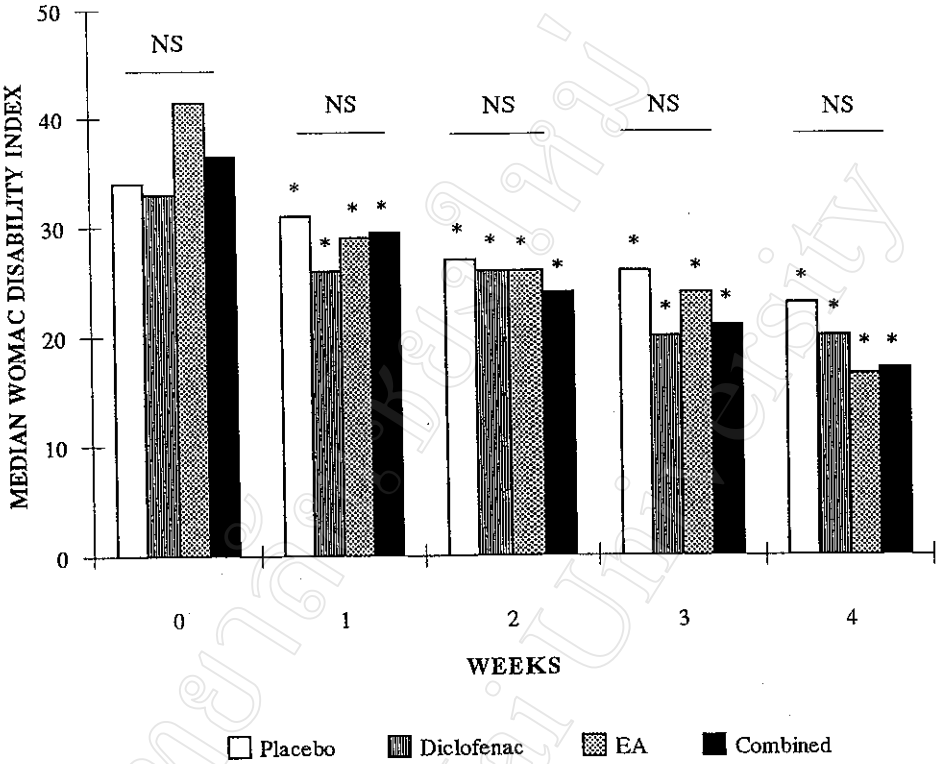

Figure 7. Median WOMAC disability index in each treatment group evaluated at the end of run-in period (week 0) and during treatment. *= $p<0.05$ within group (Wilcoxon's match paired test). NS = no significance among groups (Kruskal Wallis test).

Table 12. Median WOMAC disability index in each treatment group evaluated at the end of run-in period (week 0) and during treatment*.

Treatment groups	Time of study (weeks)				
	0	1	2	3	4
Placebo (n=45)	34 (6-63)	31† (2-62)	27† (1-66)	26† (1-60)	23† (0-59)
Diclofenac (n=49)	33 (11-68)	26† (1-58)	26† (3-52)	20† (1-43)	20† (0-47)
EA (n=46)	41.5 (10-66)	29† (7-65)	26† (2-54)	24† (0-55)	16.5† (0-50)
Combined (n=46)	36.5 (12-68)	29.5† (4-66)	24† (2-60)	21† (1-62)	17† (0-60)
p value**	0.65	0.36	0.56	0.30	0.17

* Data represent median (range).

† $p<0.05$ within group (Wilcoxon's match paired test).

** Kruskall Wallis test among the four groups.

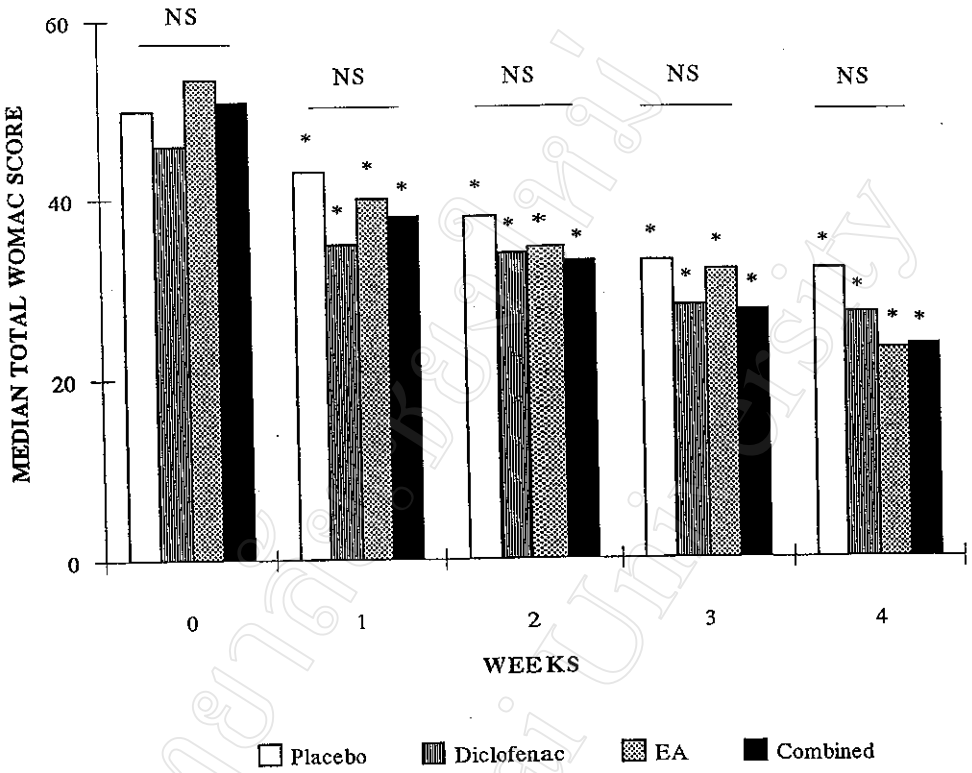

Figure 8. Median total WOMAC score (pain+stiffness+disability index) in each treatment group evaluated at the end of run-in period (week 0) and during treatment. *= $p<0.05$ within group (Wilcoxon's match paired test). NS = no significance among groups (Kruskal Wallis test).

Table 13. Median total WOMAC score (pain+stiffness+disability index) in each treatment group evaluated at the end of run-in period (week 0) and during treatment*.

Treatment groups	Time of study (weeks)				
	0	1	2	3	4
Placebo (n=45)	50 (13-87)	43† (4-85)	38† (1-93)	33† (1-82)	32† (0-82)
Diclofenac (n=49)	46 (18-96)	35† (4-84)	34† (7-70)	28† (1-63)	27† (0-66)
EA (n=46)	53.5 (14-92)	40† (9-92)	34.5† (6-76)	32† (0-76)	23† (0-70)
Combined (n=46)	51 (19-95)	38† (8-92)	33† (6-88)	27.5† (4-86)	23.5† (0-84)
p value**	0.83	0.32	0.46	0.30	0.09

* Data represent median (range).

† $p<0.05$ within group (Wilcoxon's match paired test).

** Kruskall Wallis test among the four groups.

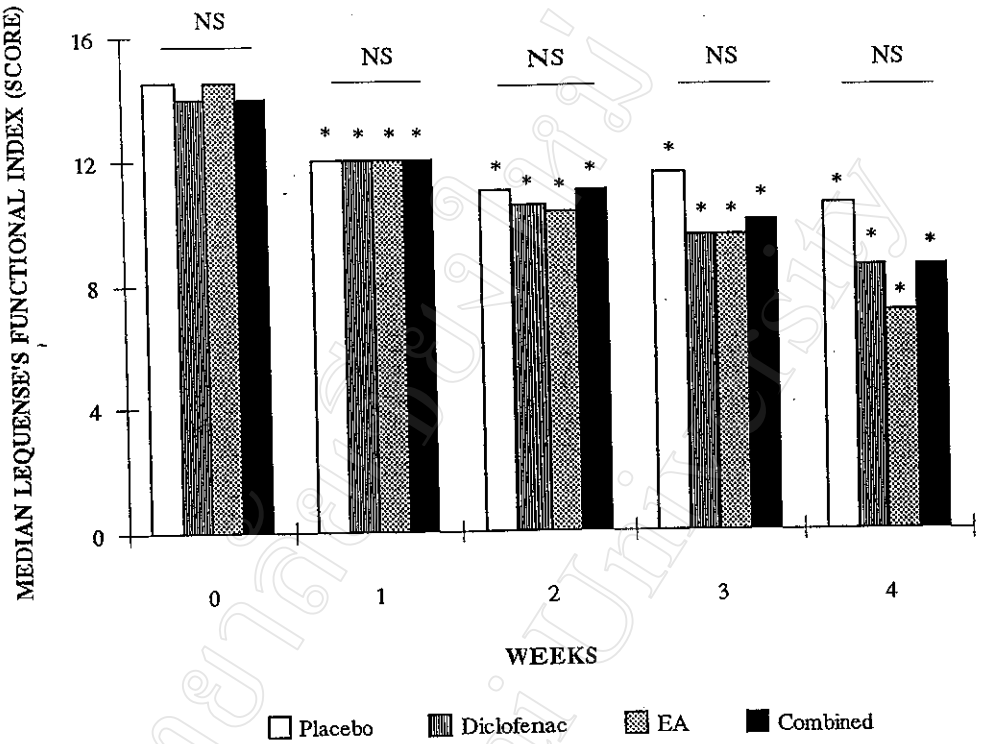

Figure 9. Median Lequesne's functional index in each treatment group evaluated at the end of run-in period (week 0) and during treatment. *= $p<0.05$ within group (Wilcoxon 's match paired test). NS = no significance among groups (Kruskal Wallis test).

Table 14. Median Lequesne's functional index in each treatment group evaluated at the end of run-in period (week 0) and during treatment*.

Treatment groups	Time of study (weeks)				
	0	1	2	3	4
Placebo (n=45)	14.5 (6-19.5)	12† (1-21)	11† (0.5-22)	11.5† (0-19.5)	10.5† (0-19.5)
Diclofenac (n=49)	14 (7-21)	12† (4-18.5)	10.5† (3-19)	9.5† (3-19)	8.5† (0-17)
EA (n=46)	14.5 (6.5-20)	12† (1.5-20.5)	10.25† (3-19)	9.5† (1-18)	7† (0-19)
Combined (n=46)	14 (8-20)	12† (2-17)	11† (2.5-17.5)	10† (1-17)	8.5† (1-17)
P value**	0.86	0.88	0.61	0.24	0.16

* Data represent median (range).

† $p<0.05$ within group (Wilcoxon's match paired test).

** Kruskal Wallis test among the four groups.

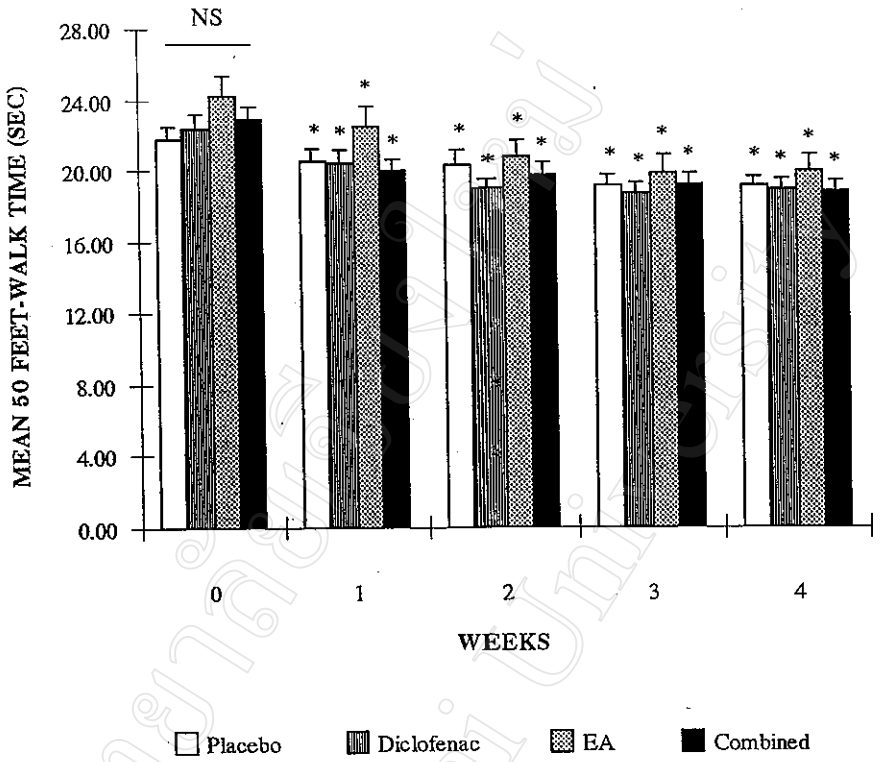

Figure 10. Mean 50 feet-walk time in each treatment group evaluated at the end of run-in period (week 0) and during treatment. Data represent mean ± SEM. *= $p<0.05$ within group (paired t-test). NS = no significance among groups (one-way ANOVA).

Table 15. Changes in 50 feet-walk time compared to the base-line values*.

Treatment groups	50 feet-walk time at week 0 (seconds)	Changes in 50 feet-walk time (seconds)			
		Week 0-1	Week 0-2	Week 0-3	Week 0-4
Placebo (n=45)	21.75 (4.71)	-1.21 (3.21)	-1.44 (4.49)	-2.63 (3.41)	-2.70 (3.49)
Diclofenac (n=49)	22.36 (6.00)	-1.91 (2.66)	-3.37 (3.66)	-3.66 (3.27)	-3.52 (3.25)
EA (n=46)	24.30 (7.60)	-1.75 (4.06)	-3.55 (4.38)	-4.50 (4.36)	-4.41 (4.72)
Combined (n=46)	22.92 (5.20)	-2.91 (3.08)	-3.22 (3.55)	-3.72 (3.47)	-4.13 (3.66)
p value**	0.21	0.10	0.05	0.12	0.15

* Data represent mean (SD).

** One-way ANOVA among the four groups.

Table 16. Orthopedist's and patient's overall opinions evaluated at week 1.

	Treatment groups				
	Placebo (n=45)	Diclofenac (n=49)	EA (n=46)	Combined (n=46)	*p* value
Orthopedist's overall opinion*					0.09[f]
Worse	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
Same	28 (62.22)	24 (48.98)	27 (58.70)	15 (32.61)	
Better	17 (37.78)	19 (38.78)	15 (32.61)	28 (60.87)	
Much better	0 (0.00)	6 (12.24)	4 (8.70)	3 (6.52)	
Patient's overall opinion*					0.51[c]
Worse	1 (2.22)	0 (0.00)	0 (0.00)	0 (0.00)	
Same	17 (37.78)	8 (16.33)	10 (21.74)	7 (15.22)	
Better	22 (48.89)	32 (65.31)	31 (67.39)	30 (65.22)	
Much better	5 (11.11)	9 (18.37)	5 (10.87)	9 (19.57)	

*Data represent number of patients (percentage in each group)

Statistical analysis: f= Fisher's exact test, c=chi-square test (evaluated on the proportions of patients with opinion of "much better").

Table 17. Orthopedist's and patient's overall opinions evaluated at week 2.

	Treatment groups				
	Placebo (n=45)	Diclofenac (n=49)	EA (n=46)	Combined (n=46)	*p* value**
Orthopedist's overall opinion*					0.11
Worse	1 (2.22)	0 (0.00)	0 (0.00)	0 (0.00)	
Same	22 (48.89)	20 (40.82)	17 (36.96)	10 (21.74)	
Better	19 (42.22)	17 (34.69)	19 (41.30)	29 (63.04)	
Much better	3 (6.67)	12 (24.49)	10 (21.74)	7 (15.22)	
Patient's overall opinion*					0.21
Worse	5 (11.11)	1 (2.04)	0 (0.00)	0 (0.00)	
Same	9 (20.00)	7 (14.29)	4 (8.70)	5 (10.87)	
Better	23 (51.11)	26 (53.06)	25 (54.35)	26 (56.52)	
Much better	8 (17.78)	15 (30.61)	17 (36.96)	15 (32.61)	

* Data represent number of patients (percentage in each group)

** Chi-square test evaluated on the proportions of patients with opinion of "much better".

Table 18. Orthopedist's and patient's overall opinions evaluated at week 3.

	Treatment groups				
	Placebo (n=45)	Diclofenac (n=49)	EA (n=46)	Combined (n=46)	*p* value**
Orthopedist's overall opinion*					0.02
Worse	1 (2.22)	0 (0.00)	0 (0.00)	0 (0.00)	
Same	15 (33.33)	8 (16.33)	7 (15.22)	6 (13.04)	
Better	23 (51.11)	26 (53.06)	20 (43.48)	30 (65.22)	
Much better	6 (13.33)	15 (30.61)	19 (41.30)	10 (21.74)	
Patient's overall opinion*					0.27
Worse	1 (2.22)	1 (2.04)	0 (0.00)	0 (0.00)	
Same	12 (26.67)	2 (4.08)	2 (4.35)	3 (6.52)	
Better	17 (37.78)	23 (46.94)	20 (43.48)	25 (54.35)	
Much better	15 (33.33)	23 (46.94)	24 (52.17)	18 (39.13)	

* Data represent number of patients (percentage in each group)

** Chi-square test evaluated on the proportions of patients with opinion of "much better".

Table 19. Orthopedist's and patient's overall opinions evaluated at week 4.

	Treatment groups				
	Placebo (n=45)	Diclofenac (n=49)	EA (n=46)	Combined (n=46)	*p* value**
Orthopedist's overall opinion					0.01
Worse	1 (2.22)	0 (0.00)	0 (0.00)	0 (0.00)	
Same	16 (35.56)	10 (20.41)	5 (10.87)	7 (15.22)	
Better	22 (48.89)	21 (42.86)	20 (43.48)	23 (50.00)	
Much better	6 (13.33)	18 (36.73)	21 (45.65)	16 (34.78)	
Patient's overall opinion					0.09
Worse	1 (2.22)	0 (0.00)	0 (0.00)	0 (0.00)	
Same	9 (20.00)	7 (14.29)	4 (8.70)	1 (2.17)	
Better	16 (35.56)	17 (34.69)	11 (23.91)	23 (50.00)	
Much better	19 (42.22)	25 (51.02)	31 (67.39)	22 (47.83)	

* Data represent number of patients (percentage in each group)

** Chi-square test evaluated on the proportions of patients with opinion of "much better".

Table 20. Number of the patients considered to be responders in each treatment group*.

Treatment groups	Time of study (weeks)			
	1	2	3	4
Placebo (n=45)	3 (6.67)	6 (13.33)	8 (17.78)	13 (28.89)
Diclofenac (n=49)	3 (6.12)	9 (18.37)	16 (32.65)	18 (36.73)
EA (n=46)	3 (6.52)	15 (32.61)	18 (39.13)	27 (58.70)
Combined (n=46)	4 (8.70)	7 (15.22)	14 (30.43)	24 (52.17)
p value	0.98[f]	0.09[c]	0.16[c]	0.02[c]

*Data represent number of patients (percentage in each group).

Statistical analysis: f= Fisher's exact test, c=chi-square test.

Table 21. Percentage of patients experienced adverse events during treatment*.

Adverse events	Treatment groups				*p* values
	Placebo (n=45)	Diclofenac (n=49)	EA (n=46)	Combined (n=46)	
No adverse events	62.22	65.31	54.35	45.65	0.22[c]
Gastrointestinal symptoms	33.33	20.41	17.39	23.91	0.31[c]
Central nervous system symptoms	2.22	6.12	0	2.17	0.38[f]
Rash	6.67	4.08	2.17	0	0.33[f]
Edema	0	4.08	4.35	0	0.34[f]
Hypertension	0	4.08	2.17	2.17	0.90[f]
Local contrusion	0	2.04	43.48	45.65	<0.001[f]

*More than one adverse events might be experienced in some patients.

Statistical analysis: c= chi-square, f= Fisher exact's test.

Table 22. Number of responders considered at the end of the study (week 4) and at 1 and 2 month(s) after treatment*.

Treatment groups	responders at week 4	1 month after treatment: remaining responders/ evaluated responders†	2 months after treatment: remaining responders/ evaluated responders†
Placebo	13	11/12	9/12
Diclofenac	18	10/16	7/15
EA	27	21/25	19/24
Combined	24	14/24	14/24
p value**		0.12	0.19

* Only the responders at the end of the study were followed up to 2 months.

† Some patients were unable to be evaluated due to loss of follow up or using NSAIDs for other purposes during follow-up period.

** Fisher exact's test among the four groups.

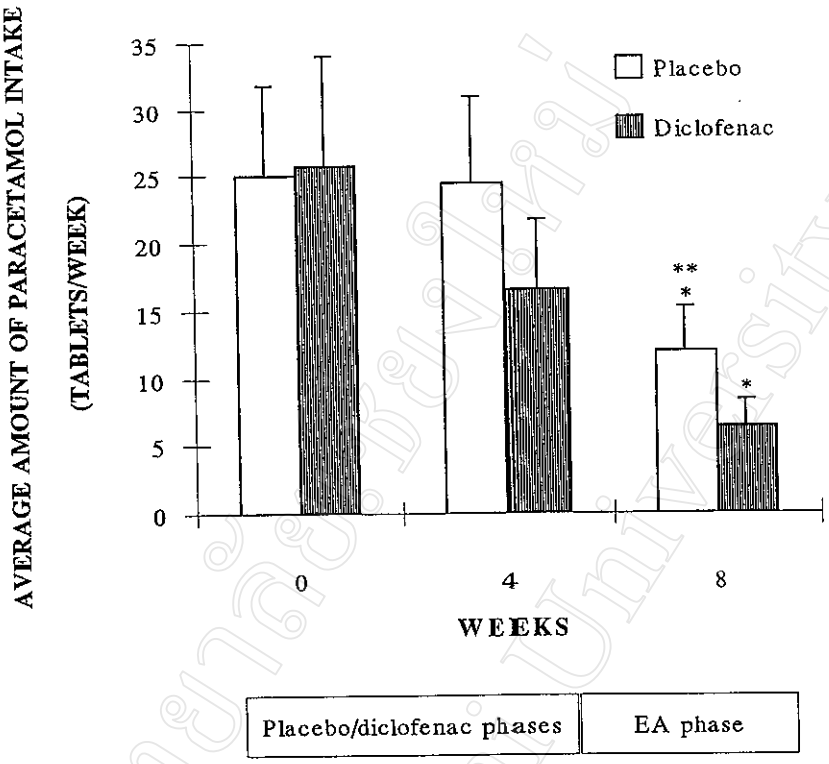

Figure 11. Average amount of paracetamol tablets taken/week during run-in period (week 0), placebo or diclofenac phases (week 4), and EA phase (week 8) in a partial cross-over study. p <0.05 within group analysis compared to base-line value (*) or value of week 4 (**).

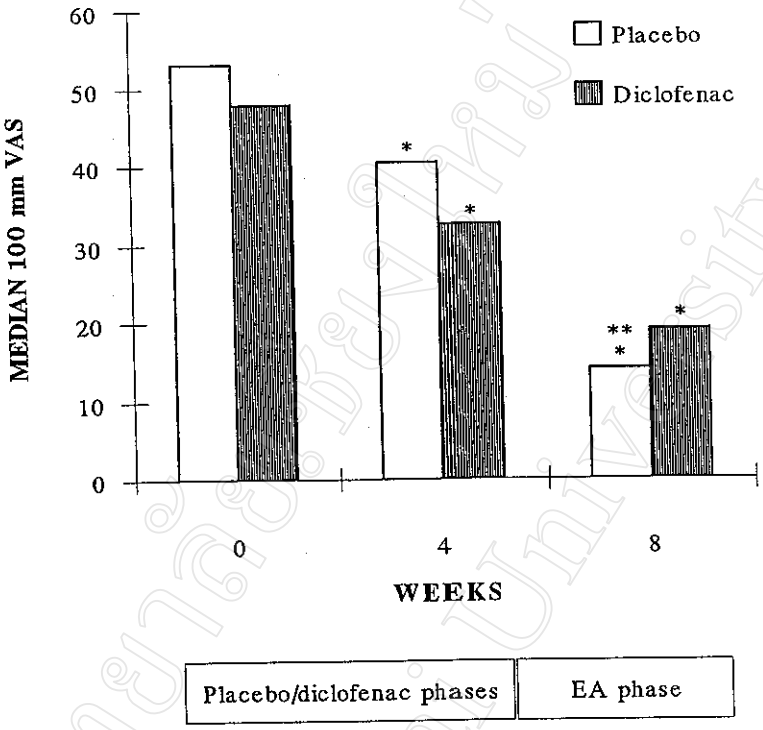

Figure 12. Median 100 mm VAS at the end of run-in period (week 0), placebo or diclofenac phases (week 4), and EA phase (week 8) in a partial cross-over study. $p < 0.05$ within group analysis compared to base-line value (*) or value of week 4 (**).

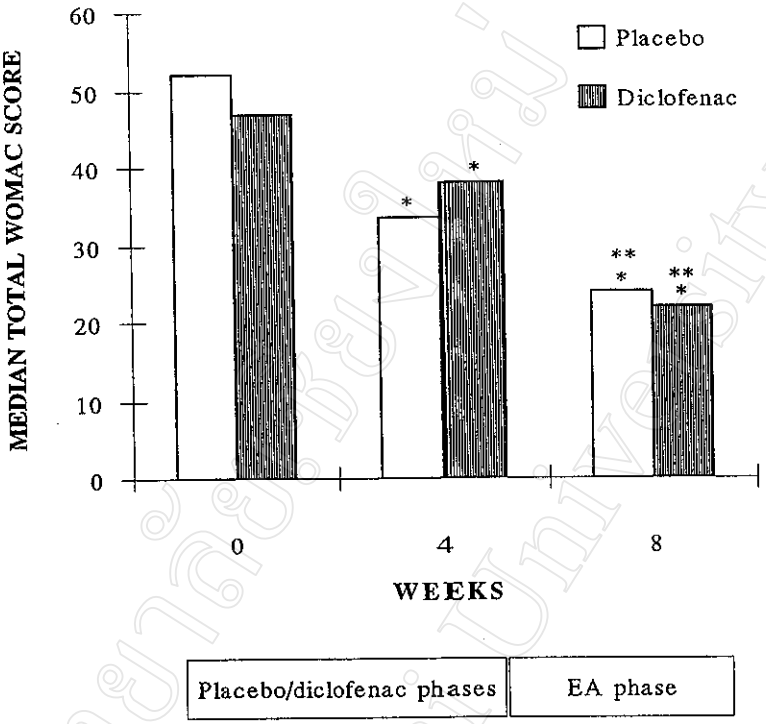

Figure 13. Median total WOMAC score at the end of run-in period (week 0), placebo or diclofenac phases (week 4), and EA phase (week 8) in a partial cross-over study. $p < 0.05$ within group analysis compared to base-line value (*) or value of week 4 (**).

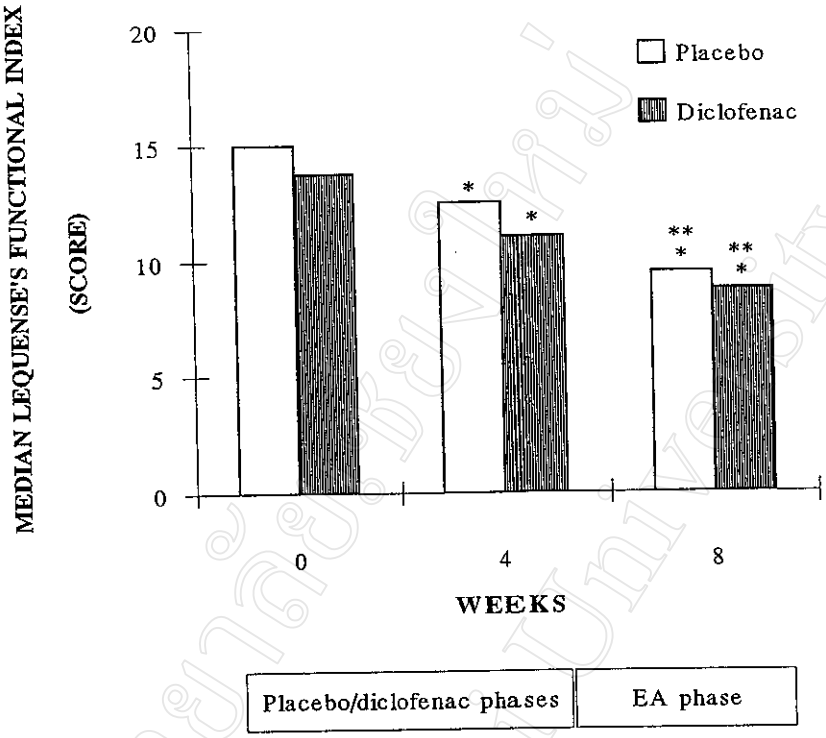

Figure 14. Median Lequense's functional index at the end of run-in period (week 0), placebo or diclofenac phases (week 4), and EA phase (week 8) in a partial cross-over study. $p < 0.05$ within group analysis compared to base-line value (*) or value of week 4 (**).

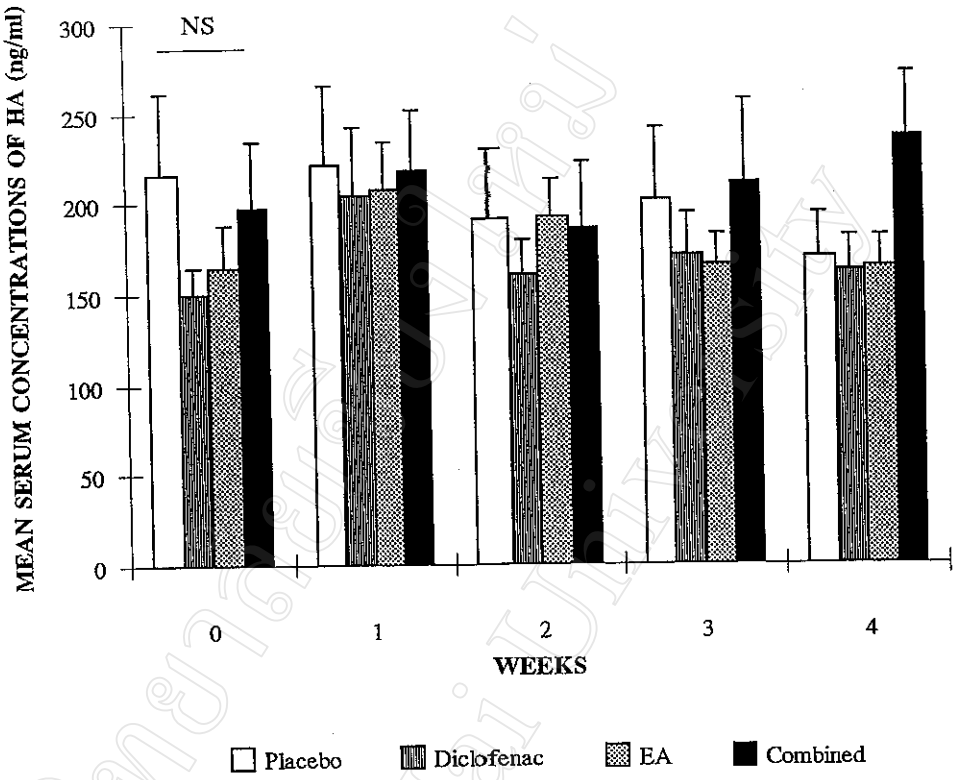

Figure 15. Mean serum concentrations of HA over time. Data represent mean ± SEM. NS = no significance among groups (one-way ANOVA).

Table 23. Changes in serum concentrations of HA compared to the base-line values.

Treatment groups	Changes in serum concentrations of HA* (ng/ml)			
	Week 0-1	Week 0-2	Week 0-3	Week 0-4
Placebo (n=45)	4.97 (46.52)	-25.70 (49.90)	-15.11 (52.78)	-46.12 (26.69)
Diclofenac (n=49)	54.42 (33.60)	11.26 (21.17)	21.24 (18.29)	12.64 (17.49)
EA (n=46)	42.74 (26.83)	27.20 (24.88)	0.43 (21.58)	-0.49 (19.65)
Combined (n=46)	20.88 (34.89)	-11.63 (38.77)	13.64 (32.02)	38.48 (26.12)
p value**	0.77	0.72	0.88	0.07

* Data represent mean (SEM).

** One-way ANOVA among the four groups.

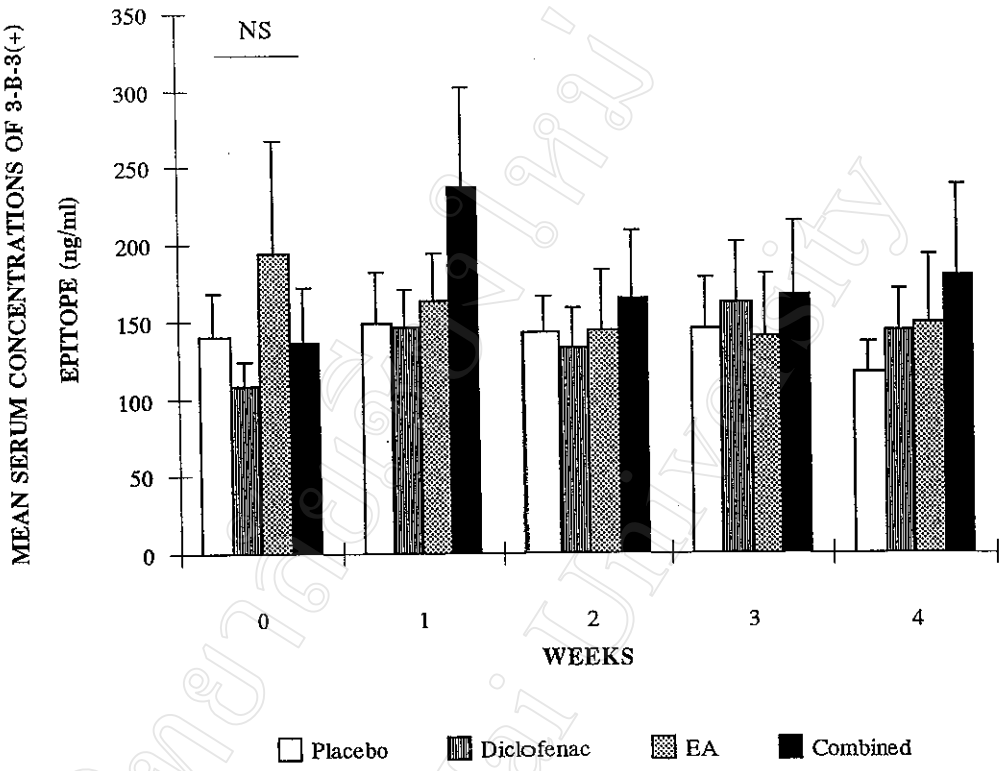

Figure 16. Mean serum concentrations of CS 3-B-3(+) epitope over time. Data represent mean ± SEM. NS = no significance among groups (one-way ANOVA).

Table 24. Changes in serum concentrations of CS 3-B-3(+) epitope compared to the base-line values.

Treatment groups	Changes in concentrations of CS 3-B-3(+) epitope* (ng/ml)			
	Week 0-1	Week 0-2	Week 0-3	Week 0-4
Placebo (n=45)	8.97 (28.19)	2.31 (26.61)	4.94 (32.37)	-22.44 (19.54)
Diclofenac (n=49)	37.98 (27.07)	24.48 (26.74)	53.87 (37.77)	35.21 (21.56)
EA (n=46)	-31.46 (57.89)	-50.40 (43.61)	-54.57 (36.73)	-45.56 (34.49)
Combined (n=46)	99.95 (57.86)	27.28 (23.18)	30.67 (23.18)	42.31 (59.03)
p value**	0.22	0.26	0.12	0.26

* Data represent mean (SEM).

** One-way ANOVA among the four groups.

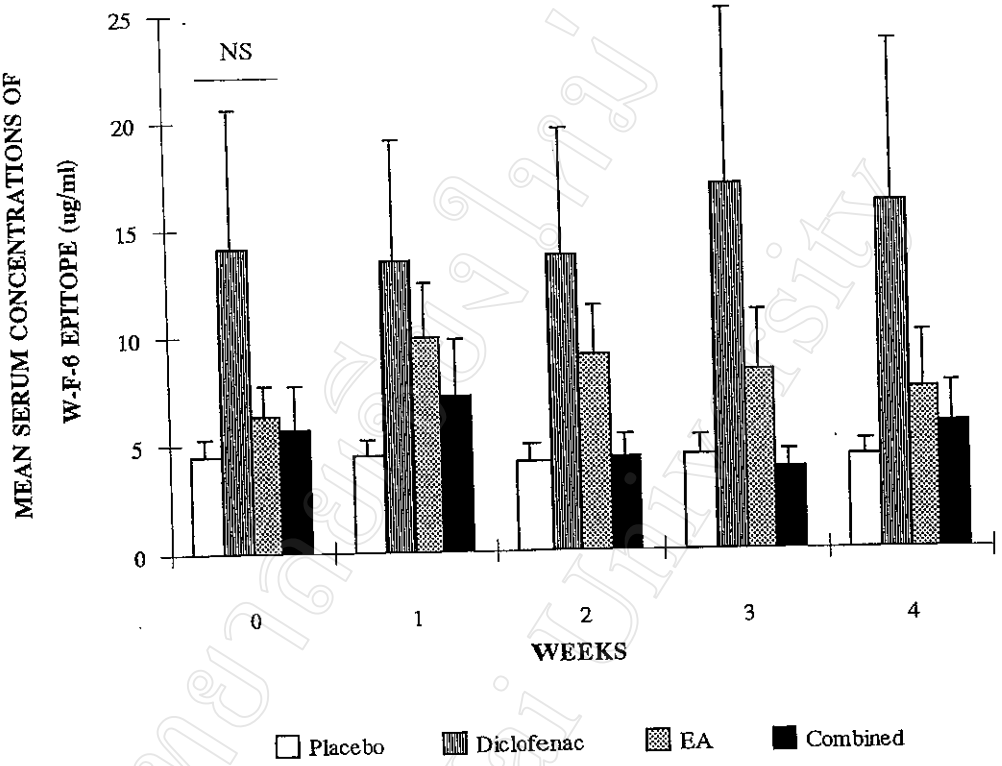

Figure 17. Mean serum concentrations of CS W-F-6 epitope over time. Data represent mean ± SEM. NS = no significance among groups (one-way ANOVA).

Table 25. Changes in serum concentrations of CS W-F-6 epitope compared to the base-line values.

Treatment groups	Changes in serum concentrations of CS W-F-6* (μg/ml)			
	Week 0-1	Week 0-2	Week 0-3	Week 0-4
Placebo (n=45)	-0.04 (0.37)	-0.40 (0.58)	-0.08 (0.70)	-0.24 (0.46)
Diclofenac (n=49)	-0.57 (1.34)	-0.40 (2.69)	2.86 (2.44)	1.98 (1.57)
EA (n=46)	3.63 (1.81)	2.69 (1.96)	1.93 (2.24)	1.08 (1.38)
Combined (n=46)	1.54 (1.91)	-1.35 (1.90)	-1.94 (1.52)	0.08 (0.68)
p value**	0.18	0.48	0.26	0.48

* Data represent mean (SEM).

** One-way ANOVA among the four groups.