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Efficacy and Safety of Different Aceclofenac Treatments for Chronic Lower Back Pain: Prospective, Randomized, Single Center, Open-Label Clinical Trials

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Purpose: Nonsteroidal anti-inflammatory drugs are a mainstay for medical treatment of chronic lower back pain (CLBP). Increased dose intervals for medication have been associated with increased patient adherence to prescriptions. The purpose of this clinical trial was to compare the efficacy and safety of a once daily dose of aceclofenac controlled release (CR) and a twice daily dose of aceclofenac for CLBP management.

Materials and Methods: A prospective, randomized, single center, open-label clinical trial was performed to compare the efficacy and safety of aceclofenac CR (200 mg once daily) to aceclofenac dose (100 mg twice daily). Fifty patients in each group were enrolled for the study. The primary end point was Visual Analogue Scale (VAS) change at baseline to that at 2 weeks after medication and safety profiles. Also, change in quality of life measured by EuroQoL 5D (EQ-5D) and Oswestry Disability Index (ODI) functional score for the lumbar spine were also assessed.

Results: Within groups at pre- and post-treatment, there were significant VAS reductions for aceclofenac CR and aceclofenac (p=0.028). EQ-5D increased significantly in both groups (p=0.037). ODI scores decreased significantly in both groups (p=0.012). However, there were no significant differences between aceclofenac CR and aceclofenac at pre- and post-treatment. Patients with aceclofenac CR showed significant increases in heartburn and indigestion and adverse gastrointestinal effects, compared to aceclofenac.

Conclusion: In patients with CLBP, aceclofenac CR and aceclofenac demonstrated significant symptomatic pain relief, improvement in quality of life and functional scores. Aceclofenac CR slightly increased gastrointestinal adverse effects, such as heartburn and indigestion.

Key Words: Chronic lower back pain, NSAIDs, aceclofenac

INTRODUCTION

Chronic lower back pain (CLBP) is prevalent worldwide in all age groups, and is associated with significant morbidity and high health care costs.[1,2] CLBP treatments are multimodal, including medication, injection, physical therapy, exercise, back school, and sometimes surgery.[3] Since surgical intervention is a last resort for CLBP, therapeutic treatment is acute and also requires patient adherence. Single or cocktail medical treatments with or without narcotics are conservative, widely accepted treatment practices. Nonsteroidal anti-inflammatory drugs (NSAIDs) are more often prescribed than muscle relaxants, antidepressants, antiepileptics, or narcotics.[4]

NSAIDs have many side effects, including adverse gastrointestinal effects, cardiovascular risk, and patient adherence.[5,6] Cyclooxygenase-2 (COX-2) inhibitors are associated with fewer NSAID-related side effects. First-line COX-2 inhibitors are rec-

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ommended for elderly patients presenting with osteoarthritis and gastrointestinal risk factors. Conventional NSAIDs can be prescribed to relatively young patients (<60 years) with musculoskeletal pain, in whom cardiovascular and gastrointestinal risk is relatively lower than patients >60 years.

Aceclofenac is a NSAID phenylacetic acid derivative {2-[(2, 6-dichlorophenyl)amino]-phenylacetoxyacetic acid} widely and safely prescribed for musculoskeletal pain associated with rheumatic, degenerative, and traumatic injury etiologies.[7-9] Furthermore, aceclofenac is effective for managing acute to CLBP, and has a wide safety profile.[10] Aceclofenac and diclofenac are classified as acetic acid NASIDs, and are not associated with adverse cardiovascular events. NSAIDs that have been associated with adverse cardiovascular events include ibuprofen, celecoxib, and rofecoxib.[11]

Dose interval is a crucial factor to assuring adherence to medical therapy. Increased dose interval has been associated with increased patient adherence to NSAID and osteoporotic medication.[12] Controlled release (CR) maintained therapeutic serum levels for longer periods of time, with less gastrointestinal insult and increased patient adherence.[13]

Accordingly, the purpose of this clinical trial was to compare the efficacy and safety of a once daily dose of aceclofenac CR and a twice daily dose of aceclofenac for CLBP management.

MATERIALS AND METHODS

Study design

A prospective, randomized, single center, open-label clinical trial was performed from February 2011 to December 2012 at an out-patient orthopedic clinic. The clinical trial protocol was approved by the Institutional Review Board of Yonsei University College of Medicine, Seoul, Korea (CR NO. 4-2010-0433). All subjects voluntarily submitted informed consent after thorough trial protocol explanation. The trial protocol was developed to compare the efficacy and safety of a once daily dose of aceclofenac CR (200 mg once daily) to a conventional twice daily aceclofenac dose (100 mg twice daily) (Fig. 1). Change in Visual Analogue Scale (VAS) (range 0–100; higher scores indicate greater pain)[14] from baseline to 2 weeks after each medication was assessed. Safety profiles, change in quality of life as measured by EuroQoL 5D (EQ-5D),[15,16] and Oswestry Disability Index (ODI)[17,18] functional score for lumbar spine were also assessed. Data were analyzed with an intention-to-treat design.

The sample size calculation was based on differences in VAS score between the groups as obtained from a previous study.[13] We calculated that a minimum of 45 patients would be needed in each treatment arm (allowing 20% dropouts) to detect a difference of at least 0.6 between groups with a two-sided type I error of 0.05 and 80% power.

Subject selection criteria

Inclusion criteria

Subjects of both genders aged 20 to 75 years reporting CLBP for at least 3 months or more, with pain intensity as measured by the VAS >40 mm, were enrolled. CLBP pain parameters included lower back pain >3 months, VAS >40 mm, CLBP with or without leg pain, daily pain attacks, and persistent pain. Plain lumbar radiographs were used to make diagnoses. Detailed procedures and hazard/benefit were carefully explained to all subjects.

Exclusion criteria

Subjects were excluded if they presented with acute fracture, malignancy, neurologic deficit, severe leg pain mandating surgery (lumbar disc herniation and spinal stenosis), fibromyalgia, compensation case, recent injection procedure, spinal surgery, history of allergy to aceclofenac, narcotic abuse, and alcohol abuse.

Outcome measures

Visual Analogue Scale

VAS mean level of back pain was assessed (0–100 mm pain scale: 0=none and 100=unbearable).

EQ-5D

EQ-5D consisted of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension had three levels of severity: 1) no problems, 2) some problems, and 3) extreme problems. EQ-5D was calculated thusly: each level of all dimensions with 1 as perfect, and 0 as worst quality of life. Current general health status was also assessed using the EQ-5D VAS (0–100, 100=best health status).

Oswestry Disability Index

The ODI is a 10-item self-report questionnaire measuring "back-specific function" with six response levels. Each item was scored from 0 to 5, higher scores being worse, which were transformed into a 0 to 100 scale. The 10 items included pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and traveling.

Table 1. Patient Demographic Data

	Aceclofenac CR	Aceclofenac	*p* value
Number of patients (n)	50	50	
Gender (male:female)	12:38	12:38	1.000*
Age	57.6±11.3	56.9±11	0.799†
Height (cm)	160.2±8.1	159.6±7.7	0.695†
Weight (kg)	62.3±8.7	61.6±8.7	0.978†
Duration of back pain	50.0±55.1	91.6±119.0	0.184†

CR, controlled release.
*Chi-square test, †Unpaired t-test.

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Table 2. Change of Pain in VAS, EQ-5D, EQ-5D VAS, and ODI

100-mm VAS score	Aceclofenac CR (n=50) Mean±SD	In group	Aceclofenac (n=50) Mean±SD	In group	Between group
Pre treat	58.2±14.0		64.0±13.1		p=0.075†
Post treat	35.7±17.1	p=0.028*	45.5±20.8	p=0.013*	p=0.109†
Alteration	22.6±15.8		18.6±17.7		p=0.145†
EQ-5D VAS	**Aceclofenac CR (n=20) Mean±SD**	**In group**	**Aceclofenac (n=20) Mean±SD**	**In group**	**Between group**
Pre treat	60.0±15.1		62.7±14.1†		p=0.245†
Post treat	65.0±22.5	p=0.071*	68.5±13*†	p=0.082*	p=0.125†
Alteration	5.0±14.7		5.8±16.7		p=0.249†
EQ-5D	**Aceclofenac CR (n=50) Median (IQR)**	**In group**	**Aceclofenac (n=50) Median (IQR)**	**In group**	**Between group**
Pre treat	0.5 (0.3–0.7)		0.5 (0.3–0.7)		p=0.423§
Post treat	0.7 (0.5–0.9)	p=0.037‡	0.6 (0.4–0.8)	p=0.042‡	p=0.359§
Alteration	0.2 (0.1–0.4)		0.1 (-0.1–0.3)		p=0.438§
ODI	**Aceclofenac CR (n=50) Median (IQR)**	**In group**	**Aceclofenac (n=50) Median (IQR)**	**In group**	**Between group**
Pre treat	34.6 (21.8–47.4)		37.1±13.3 (23.8–50.4)		p=0.097§
Post treat	23.8 (11.1–36.5)	p=0.012‡	27.3±12.7 (14.6–40.0)	p=0.026‡	p=0.165§
Alteration	10.6 (-1.0–22.2)		10.4±12.9 (-2.5–23.3)		p=0.581§

CR, controlled release; VAS, Visual Analogue Scale; EQ-5D, EuroQoL 5D; EQ-5D VAS, EuroQoL 5D Visual Analogue Scale; ODI, Oswestry Disability Index.
Values of VAS and EQ-5D VAS are expressed as mean with standard deviation (SD). Values of EQ-5D and ODI are expressed as median with an inter-quartile range (IQR) in parenthesis. p<0.05: statistically significant.
*Paired t-test: to compare VAS, EQ5D VAS of pre- and post-treatment in each group, †Unpaired t-test: to compare VAS, EQ5D VAS between aceclofenac CR and aceclofenac groups, ‡Mann-Whitney U test: to compare EQ-5D, ODI change of pre-and post-treatment in each group, §Wilcoxon signed rank test: to compare EQ-5D, ODI change between aceclofenac CR and aceclofenac groups.

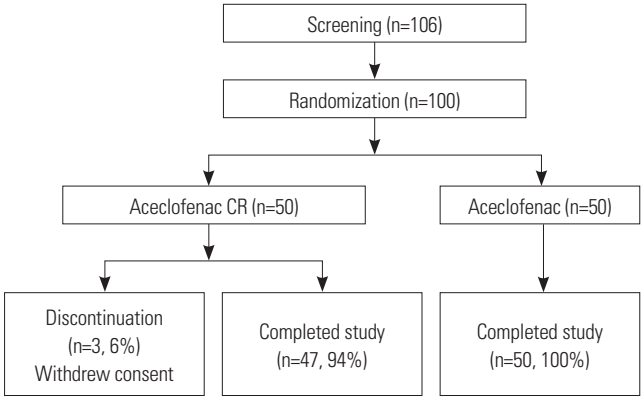

Fig. 1. Screening, randomization, and follow-up of clinical trial. CR, controlled release.

Gastrointenstinal assessment

A separate questionnaire was utilized to assess post-treatment gastrointestinal symptoms. The following six items were included: indigestion, heartburn, nausea, vomiting, abdominal pain, and diarrahea graded as 1, 2, or 3 (minimal to severe symptoms limiting daily activities).

Statistical analysis

Values of VAS and EQ-5D VAS are expressed as mean with standard deviation, and values of EQ-5D and ODI are expressed as median with an inter-quartile range (IQR). To compare pain reduction in VAS and change in EQ-5D VAS after treatment, paired t-test was utilized. Quality of life improvement as EQ-5D and ODI were analyzed by using non-parametric statistics, such as Mann-Whitney U test, to compare changes in EQ-5D and ODI pre-and post-treatment in each group and Wilcoxon's rank sum test to compare changes in EQ-5D and ODI between aceclofenac CR and aceclofenac groups. To compare gastrointestinal symptoms and adverse effects between groups, Fisher's exact test was used. Significance level was set as p<0.05.

Table 3. Gastrointenstinal Symptom Assessment

Gastrointestinal symptom	Aceclofenac CR (n=47)	Aceclofenac (n=50)	p value
Indigestion, n (%)	4 (8.5)	1 (2.0)	0.195
Heartburn, n (%)	10 (21.3)	3 (6.0)	0.037
Nausea, n (%)	2 (4.3)	1 (2.0)	0.610
Vomit, n (%)	1 (2.1)	0 (0.0)	0.485
Abdominal pain, n (%)	2 (4.3)	0 (0.0)	0.232
Diarrahea, n (%)	1 (2.1)	0 (0.0)	0.485

CR, controlled release.

RESULTS

Of 106 subjects screened with the criteria described above, 100

subjects were assigned to either aceclofenac CR (200 mg once daily) or conventional aceclofenac (100 mg twice daily) groups. There were 50 subjects in each group. During the study, only three subjects from the aceclofenac CR group dropped out of the study; all 50 aceclofenac subjects completed the study.

Before treatment, there were no differences between groups in demographic characteristics, duration of lower back pain, VAS, EQ-5D, or ODI (Table 1 and 2).

Table 4. Adverse Events

System organ class	Preferred term		*p* value
	Aceclofenac CR (n=50)	Aceclofenac (n=50)	
	Adverse events	Adverse events	
Gastrointestinal disorders, n (%)	10 (21.2)	7 (14.0)	0.595
Dyspepsia	10 (21.2)	4 (8.0)	
Nausea	2 (4.2)	1 (2.0)	
Constipation	2 (4.2)	0 (0.0)	
Abdominal pain	2 (4.2)	0 (0.0)	
Abdominal distension	0 (0.0)	2 (4.0)	
Vomiting	1 (2.1)	0 (0.0)	
Diarrhea	1 (2.1)	0 (0.0)	
Skin and subcutaneous tissue disorders, n (%)	5 (10.6)	5 (10.0)	>0.999
Swelling face	3 (6.4)	3 (6.0)	
Pruritus	1 (2.1)	1 (2.0)	
Skin disorder	1 (2.1)	0 (0.0)	
Acne	0 (0.0)	1 (2.0)	
General disorders and administration site conditions, n (%)	9 (19.2)	1 (2.0)	0.016
Generalized edema	5 (10.6)	0 (0.0)	
Swelling	1 (2.1)	1 (2.0)	
Edema peripheral	1 (2.1)	0 (0.0)	
Edema	1 (2.1)	0 (0.0)	
Face edema	1 (2.1)	0 (0.0)	
Nervous system disorders, n (%)	3 (6.4)	4 (8.0)	>0.999
Somnolence	2 (4.3)	1 (2.0)	
Paresthesia	0 (0.0)	2 (4.0)	
Dizziness	0 (0.0)	1 (2.0)	
Headache	1 (2.1)	0 (0.0)	
Investigations, n (%)	0 (0.0)	4 (8.0)	0.117
Aspartate aminotransferase increased	0 (0.0)	2 (4.0)	
Gamma-glutamyltransferase increased	0 (0.0)	2 (4.0)	
Alanine aminotransferase increased	0 (0.0)	1 (2.0)	
Infections and infestations, n (%)	1 (2.1)	1 (2.0)	>0.999
Nasopharyngitis	0 (0.0)	1 (2.0)	
Oral herpes	1 (2.1)	0 (0.0)	
Musculoskeletal and connective tissue disorders, n (%)	2 (4.3)	0 (0.0)	0.495
Pain in extremity	1 (2.1)	0 (0.0)	
Musculoskeletal pain	1 (2.1)	0 (0.0)	
Vascular disorders, n (%)	1 (2.1)	0 (0.0)	>0.999
Flushing	1 (2.1)	0 (0.0)	
Renal and urinary disorders, n (%)	1 (2.1)	0 (0.0)	>0.999
Pollakiuria	1 (2.1)	0 (0.0)	
Eye disorders, n (%)	0 (0.0)	1 (2.0)	>0.999
Abnormal sensation in eye	0 (0.0)	1 (2.0)	
Cardiac disorders, n (%)	1 (2.1)	0 (0.0)	>0.999
Palpitations	1 (2.1)	0 (0.0)	

CR, controlled release.

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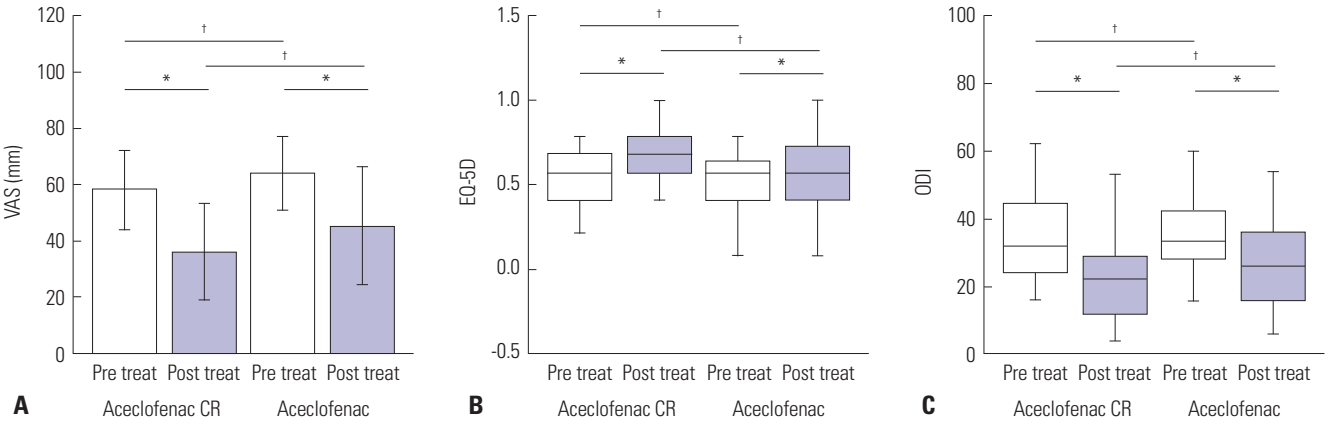

Fig. 2. (A) Change in Visual Analogue Scale (VAS) presented as mean±standard deviation. (B) Change in calculated EuroQoL 5D (EQ-5D) presented as median and interquartile range (IQR). (C) Change in Oswestry Disability Index (ODI), presented as median and IQR. Comparison between aceclofenac controlled release (CR; 200 mg once daily) and conventional aceclofenac (100 mg twice daily) showed there was significant reduction of pain and ODI score, and increase in EQ-5D for each group at 2 weeks, however, there was no difference between groups pre- and post-treatment for VAS, ODI, and EQ-5D. *p<0.05, †Non-significant.

VAS (0–100 mm) pain intensity was significantly reduced in both groups: aceclofenac CR, before 58.2±14.0, after 35.7±17.1, p<0.05; aceclofenac, before 64.0±13.1, after 45.5±20.8, p<0.05. There was no significant difference in pain intensity between groups pre- and post-treatment (Table 2, Fig. 2A).

Quality of life as measured by calculated EQ-5D increased significantly in aceclofenac CR [before 0.5 (0.3–0.7), after 0.7 (0.5–0.9), p<0.05] and aceclofenac groups [before 0.5 (0.3–0.7), after 0.6 (0.4–0.8), p<0.05]. By contrast, there were no signficant differences in EQ-5D general health status between aceclofenac CR and aceclofenac groups pre- and post-treatment. All EQ-5D dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), except self-care in the aceclopenac group, showed level increases (Table 2, Figs. 2B and 3).

ODI spinal functional score decreased significantly in both aceclofenac CR [before 34.6 (21.8–47.4), after 23.8 (11.1–36.5), p<0.05] and aceclofenac groups [before 37.1±13.3 (23.8–50.4), after 27.3±12.7 (14.6–40.0), p<0.05]. In contrast, there was no signficant difference between groups for other ODI items pre- and post-treatment (Table 2, Fig. 2C).

Gastrointenstional assessment revealed the aceclofenac CR group presented with more complaints than the aceclofenac group for all items: indigestion (4 vs. 1), heartburn (10 vs. 3) (p<0.05), nausea (2 vs. 1), vomiting (1 vs. 0), abdominal pain (2 vs. 0), and diarrahea (1 vs. 0). Among items of gastrointenstional assessment, only heartburn showed significant increase in aceclofenac CR group (p<0.05). However, the aceclofenac CR group presented only five complaints at the most severe symptom level, while the remaining 15 were at minimal and tolerable levels (Table 3).

Adverse effects post aceclofenac CR and aceclofenac treatment are presented in Table 4. In mutiple categories (gastrointestinal, skin and subcutaneous, general physical, nervous system, serologic, infectious, musculoskeletal, vascular, renal, ocular, and cardiac) there were no significant differences in adverse effects between groups, except edema and swelling in general disorders and administration site conditions (p<0.05).

DISCUSSION

Both aceclofenac CR and aceclofenac were associated with significant pain reduction, increase in quality of life, improvement in spinal function, and tolerable minor adverse effects. For all measures only EQ-5D VAS showed no significant change pre- to post-treatment.

There was significant VAS reduction for aceclofenac CR (22.6) and aceclofenac (18.6), which was significant within groups pre- and post-treatment; however, there was no significant difference between groups pre- and post-treatment. Furthermore, increase in quality of life as calculated by EQ-5D was also significant within both groups. Alpha was set at 0.05, but p=0.10 for EQ-5D increase for both groups. Also, both groups showed significant improvement in ODI spinal functional score. There was no significant difference between groups in all ODI categories. A questionnaire specifically assessing gastrointestinal symptoms showed increased overall gastrointestinal complaints in both groups: aceclofenac CR (19 complaints) and aceclofenac (5 complaints). However, rate of heartburn was statistically significantly higher in the aceclofenac CR group. This protocol did not provide any gastrointestinal medications to protect stomach and duodenum mucosa, hence a single daily dose of aceclofenac CR (200 mg) might result in greater acidic insult to gastric mucosa than the lower twice daily dose (100 mg). There were no serious gastrointestinal effects seen in either group during the study interval. Among gastrointestinal complaints (20 incidences) on a questionnare specilized for gastrointestinal symptoms in the aceclopenac CR group, only five complaints were severe in intensity, while the

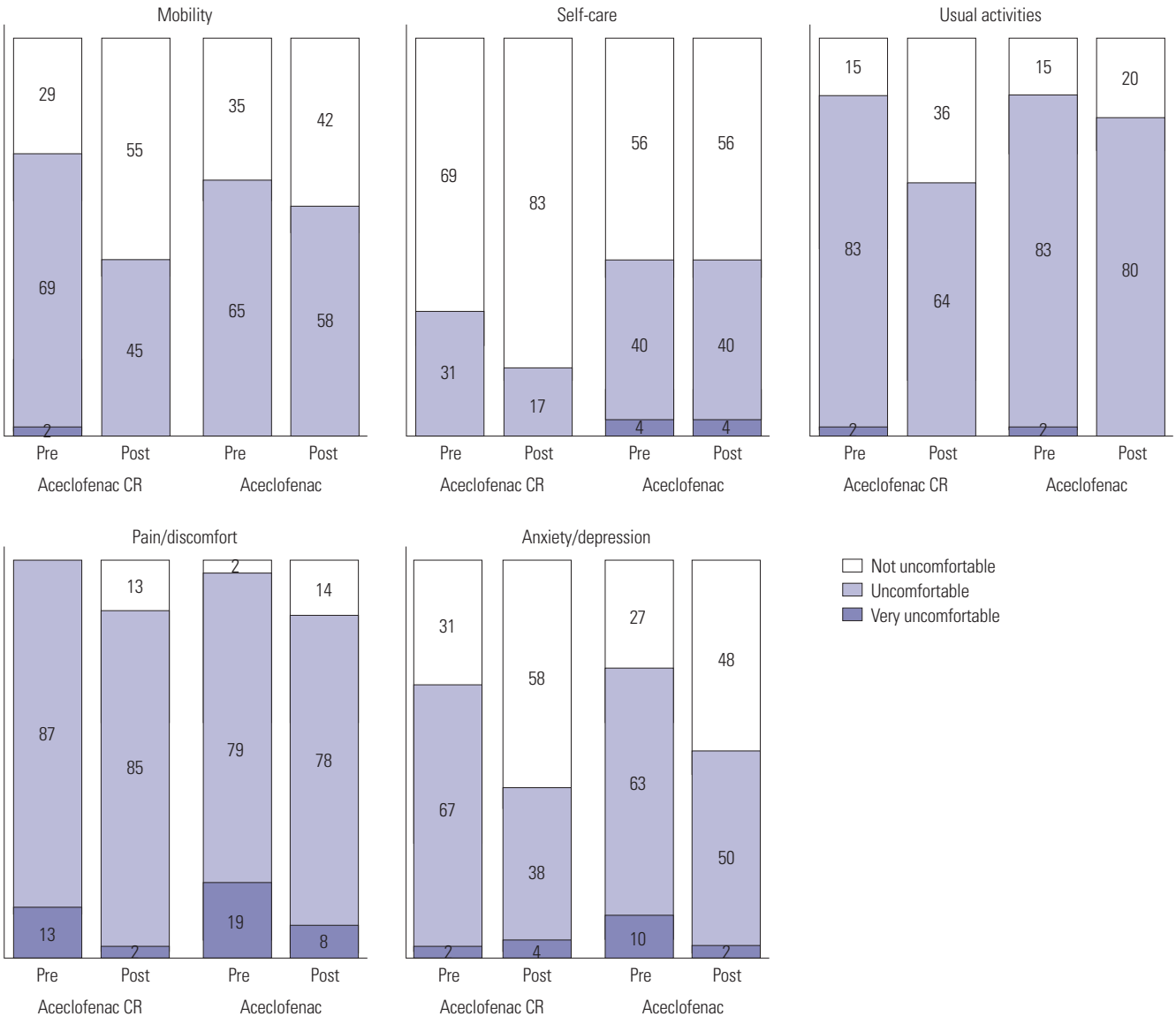

Fig. 3. Change in each dimension (mobility, self-care, usual activity, pain/discomfort, anxiety/depression) for EuroQoL 5D pre- to post-treatment with aceclofenac CR (200 mg once daily) and conventional aceclofenac (100 mg twice daily) over the 2 week trial. With the exception of self-care in the aceclofenac group, all dimensions showed improvement post-treatment. CR, controlled release.

remaning 15 complaints were minial intensity. Even though patients were enrolled in randomized fashion, duration of CLBP is different between aceclofenac CR and aceclofenac. Since CLBP is defined as lower back pain for more than 3 months, several outliers, such as CLBP more than years, seem to provide differences between groups. However, the duration of CLBP between group was statistically insignificant and chronicity of lower back pain seemed to have little effect on aceclofenac intervention, as shown in the results of uniform improvement in pain scale and quality of life measurements.

In conclusion, this prospective, randomized, single center, open-level aceclofenac CR and aceclofenac clinical trial in subjects with CLBP showed both dose regimens resulted in effective symptomatic pain relief, improvement in quality of life and functional scores, and tolerable adverse gastrointestinal effects.

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