Integrative Medicine Research 13 (2024) 101090

Contents lists available at ScienceDirect

Integrative Medicine Research

journal homepage: www.elsevier.com/locate/imr

Original Article

Clinical research on the effectiveness and safety of Uchasingihwan for low back pain with radiculopathy caused by herniated intervertebral disc of the lumbar spine: A multicenter, randomized, controlled equivalence trial

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ARTICLE INFO

Keywords:
Uchasingihwan
Herbal medicine
Lumbar disc herniation
Low back pain
Radiculopathy

ABSTRACT

Background: This study aimed to establish the clinical evidence regarding the effectiveness and safety of Uchasingihwan (UCSGH) in improving pain, function, and quality of life in patients with lumbar herniated intervertebral disc (LHIVD).

Methods: This was a multicenter, randomized, controlled, equivalence trial with two parallel arms. Seventy-four participants with LHIVD were recruited and randomly allocated to the experimental and control groups. The participants in each group took 2.5 g of UCSGH granule or loxoprofen 60 mg tablet three times a day for six weeks. Additionally, both groups received the same acupuncture treatment once a week for six weeks. Outcomes about effectiveness and safety were assessed at baseline and 3, 6, and 10 weeks after screening.

Results: As the primary outcome, the mean differences with a 95 % confidence interval (CI) of changes in low back pain between the two groups at weeks 6 (95 % CI:9.26, 8.37) and 10 (95 % CI:9.03, 9.62) from baseline were within the equivalence limit. Also, changes in radiating pain at weeks 6 (95 % CI:1.70, 15.69) and 10 (95 % CI:4.72, 13.75) were within the equivalence limit. Outcome measures for function and quality of life also showed no statistical difference. Regarding safety, the frequency of adverse events related to intervention was lower in UCSGH.

Conclusion: UCSGH showed the equivalent level of effectiveness as loxoprofen in reducing low back and radiating pain in LHIVD patients and showed sufficient safety to be used as a complementary treatment option.

Trial registration: ClinicalTrials.gov (NCT03386149), CRIS (KCT0002848).

1. Introduction

A lumbar herniated intervertebral disc (LHIVD) is a disease caused by a displacement of the nucleus pulposus or annulus fibrosis beyond intervertebral disc space. A herniated disc causes pain, numbness, and weakness in the lower back or lower extremities by compressing the dural sac or nerve root.[1,2] As low back and radiating pain caused by LHIVD seriously interferes with the daily life and occupational activity of patients. The prevalence of lumbar disc herniation is estimated to be approximately 1–3 % of adults, and the social cost of this in the United States is known to reach billions of dollars annually.[2,3] Pain management is a major concern in the conservative treatment for LHIVD.[2,4] However, conventional oral medication did not show sufficient evidence in evidence-based guidelines.[5]

Herbal medicines have been used in Asian countries for the treatment of musculoskeletal diseases and neuropathic pain, including LHIVD, and their effectiveness has been reported continuously in several studies.[6–8] Uchasingihwan (UCSGH, Korean commercial product name 'Bosinji,' and Japanese commercial product name Goshajinkigan by Tsumura & Co.), which was described in a medical book called "Je-Saeng-Bang"

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https://doi.org/10.1016/j.imr.2024.101090
Received 26 March 2024; Received in revised form 22 September 2024; Accepted 29 September 2024
Available online 30 September 2024

written in the 13th century, is one of the herbal descriptions approved for low back and lower extremity pain by Ministry of Food and Drug Safety of Korea.[9] UCSGH showed clinical effectiveness on LHIVD in observational studies.[10,11] One randomized controlled trial (RCT) reported that the effectiveness of Bosinji was similar to that of non-steroidal anti-inflammatory drugs (NSAIDs) for low back pain and paresthesia in the lower extremities; however, there were many unclear risks of bias and methodological limitations to establish sufficient evidence.[12]

Therefore, to establish clinical evidence regarding the effectiveness and safety of UCSGH in treating low back and radiating pain caused by LHIVD, we evaluated the its equivalence to NSAIDs in a rigorously designed, full-scale RCT protocol that includes assessments of pain, function, and quality of life (QoL).

2. Methods

2.1. Study protocol

This protocol was approved by the institutional review boards of the four institutions (approval numbers: KHNMCOH 2017–08–002, KHUMC 170,918-HR-039, DUBOH 2017–0007, and DHUMC-d-17,019) and published as a journal article.[13] The trial was registered at clinicaltrials.gov (registration number: NCT03386149) and in the Clinical Research Information Service (registration number: KCT0002848). This manuscript was reported to comply with the Consolidated Standards of Reporting Trials 2010 Statement.[14]

2.2. Study design

This study was a multicenter, open-label, randomized, controlled equivalence trial with two parallel arms (1:1 ratio). The trial was conducted at the Kyung Hee University Hospital at Gangdong (KHUHGD), Kyung Hee University Medical Center (KHUMC), Dongguk University Bundang Oriental Hospital (DUBOH), and Daegu Korean Medicine Hospital of Daegu Haany University (DKMHDHU). The effectiveness and safety of UCSGH in patients with low back pain with radiculopathy due to LHIVD were evaluated by comparison with loxoprofen, one of the NSAIDs.

2.3. Participants

2.3.1. Inclusion criteria

The inclusion criteria for this study were as follows: (1) age over 19 years; (2) radiating pain consistent with abnormalities in the lumbar spine that are more severe than bulging, as shown on computerized tomography or magnetic resonance imaging;[15,16] (3) low back pain score between 40 and 80 points on the 100-mm pain visual analogue scale (VAS); and (4) voluntary participation and provision of a signed informed consent form after a detailed explanation of the clinical trial has been provided.

2.3.2. Exclusion criteria

Participants who have the following characteristics were excluded: (1) congenital abnormalities or surgical history in the lumbar region; (2) red flag signs that may indicate cauda equina syndrome, such as bladder and bowel dysfunction or saddle anesthesia; (3) tumor, fracture, or infection in the lumbar region; (4) injection in the lumbar region within one week of the screening; (5) psychiatric disorders currently being treated, such as depression or schizophrenia; (6) liver function abnormality (aspartate transaminase [AST] or alanine transaminase [ALT] >100 U/L for men/70 U/L for women); (7) renal function abnormality (serum creatinine >2.0 mg/dL); (8) other diseases that could affect or interfere with therapeutic outcomes including severe gastrointestinal disease, cardiovascular disease, hypertension, diabetes, renal disease, liver disease, or thyroid disorder; (9) contraindications for NSAIDs, including concurrent disease, hypersensitivity reaction, or other medication; (10) conditions for which acupuncture is contraindicated, e.g., skin disease or hemostatic disorder (international normalized ratio >2.0 or taking anticoagulant); (11) pregnancy, breastfeeding, or having pregnancy plans; (12) other conditions for which herbal medicine treatment is contraindicated; and (13) participation in other clinical trials within one month of the screening.

2.4. Randomization and blinding

A total of 74 participants with LHIVD were recruited at four institutions (KHUHGD: 20, KHUMC: 18, DUBOH: 18, and DKMHDHU: 18). Those who agreed and signed the informed consent form were screened. If they met the eligibility criteria, the participants were randomly allocated to the experimental or control group in a 1:1 ratio according to a block randomization with a random block size of 2, 4, or 6. The randomization sequence was generated by an independent statistician using the package “blockrand” 1.3 of R (The R Foundation for Statistical Computing, Vienna, Austria). Sealed, opaque envelopes containing random codes were sent to each institution for allocation concealment. The clinical research coordinator opened the envelope and allocated participants to their groups. Blinding of participants was not possible due to differences in the form of herbal medicine granules and tablets, and blinding was performed by blocking information on group assignments to the assessors and statisticians.

2.5. Interventions

After random allocation, each group received a 6-week treatment, and outcome measures were assessed at 3, 6, and 10 weeks after screening.

Participants in the experimental group orally took 2.5 g of UCSGH granule (1.523 g of UCSGH extract, Tsumura Co., Tokyo, Japan) three times a day, 30 min after every meal for six weeks. The composition of UCSGH is listed in Supplementary Table 1.

Participants in the control group took a Loxonin tablet (60 mg of loxoprofen, Dong Wha Pharm Co., Ltd, Seoul, Korea) three times a day, 30 min after each meal, for six weeks.

As a concurrent treatment, acupuncture treatment was conducted weekly for both groups during the medication period. The details of the acupuncture treatment were reported according to the Standards for Reporting Interventions in Clinical Trials of Acupuncture. (Supplementary Table 2)

2.6. Outcome measures

All assessments were conducted by blinded independent researchers who were not involved in the intervention. The primary outcome was a change in VAS for low back pain. The secondary outcomes were evaluated using the VAS for radiating pain, Oswestry disability index (ODI), Roland-Morris disability questionnaire (RMDQ), EQ-index and EQ-VAS from EuroQol 5 Dimensions 5 Levels (EQ-5D-5 L), and global perceived effect (GPE). Assessments were conducted at weeks 0 (baseline), 3, 6 (primary endpoint), and 10 (follow-up sessions). Additionally, all adverse events were collected at every visit.

2.7. Sample size calculation

The sample size was calculated based on a previous similar study (assuming $\sigma = 9.18$, $\mu_c - \mu_t = 10$),[12] and the equivalence margin for the primary outcome was set at 18.[17] With a 0.05 significance level ($\alpha = 0.025$), 90 % power, and 1:1 ratio, we calculated the adequate sample size using the following formula[18]:

$$n = (\lambda + 1)\sigma^2\left(Z_{1-\beta} + Z_{1-\alpha}\right)^2 / \lambda\left(\mu_c - \mu_t - d\right)^2$$

Finally, we determined that the sample size required in each group should be 37 participants by considering a 20 % dropout rate with 95 % compliance. The 74 participants were recruited separately at the four research sites; each recruited the following participants: KHUHGD: 20, KHUMC: 18, DUBOH: 18, and DKMHDHU: 18.

2.8. Adverse events

The following laboratory tests about safety of drugs were carried out at the pre-screening point and at week 6 when the medication treatment was completed: complete blood count (white blood cells, red blood cells, hemoglobin, hematocrit, and platelet), liver function test (total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, and γ-glutamyl transferase), renal function test (uric acid, blood urea nitrogen [BUN], and creatinine), fasting plasma glucose, prothrombin time, activated partial thromboplastin time, erythrocyte sedimentation rate, C-reactive protein, and urine analysis (color, specific gravity, pH, protein, glucose, ketone, urobilinogen, bilirubin, nitrite, blood, and white blood cell). AST, ALT, BUN, and creatinine were also examined in week 3.

At each visit, the researchers collected information about adverse events (AEs) and drug changes. Before the pre-trial screening, the participants were given information about expected AEs listed in the informed consent form. If AEs occur, the principal investigator evaluates the severity of the incident and its relation to the interventions and provides proper examination and treatment by the compensation rules.

2.9. Statistical analysis

The data was corrected using the "last observation carried forward" method and then analyzed using the "intention-to-treat" principle, which analyzed all participants who underwent intervention at least once. The independent *t*-test and chi-square test were used to compare the differences in general characteristics between groups. Equivalence was assessed for changes in the 100-mm VAS for low back pain and radiating pain between the two groups compared to before and after treatment based on the equivalence margin of 18 mm and 95 % confidence interval (CI). Other results were analyzed using an independent *t*-test between two groups, and trends over time and time-by-treatment interactions were analyzed using a repeated measures analysis of variance. All statistical analyses were performed using PASW statistics 18 for Windows, and the statistical significance level of all statistics except the equivalence tests was set at 0.05.

3. Results

3.1. Participants

Eighty-one study participants were screened, and 74 who met the eligibility criteria were randomly assigned to two groups equally. One participant in the control group, who did not take any allocated medication, was excluded from the analysis (Fig. 1).

The two groups had no significant differences in the general characteristics, including sex, age, duration from onset, side of radiating pain,

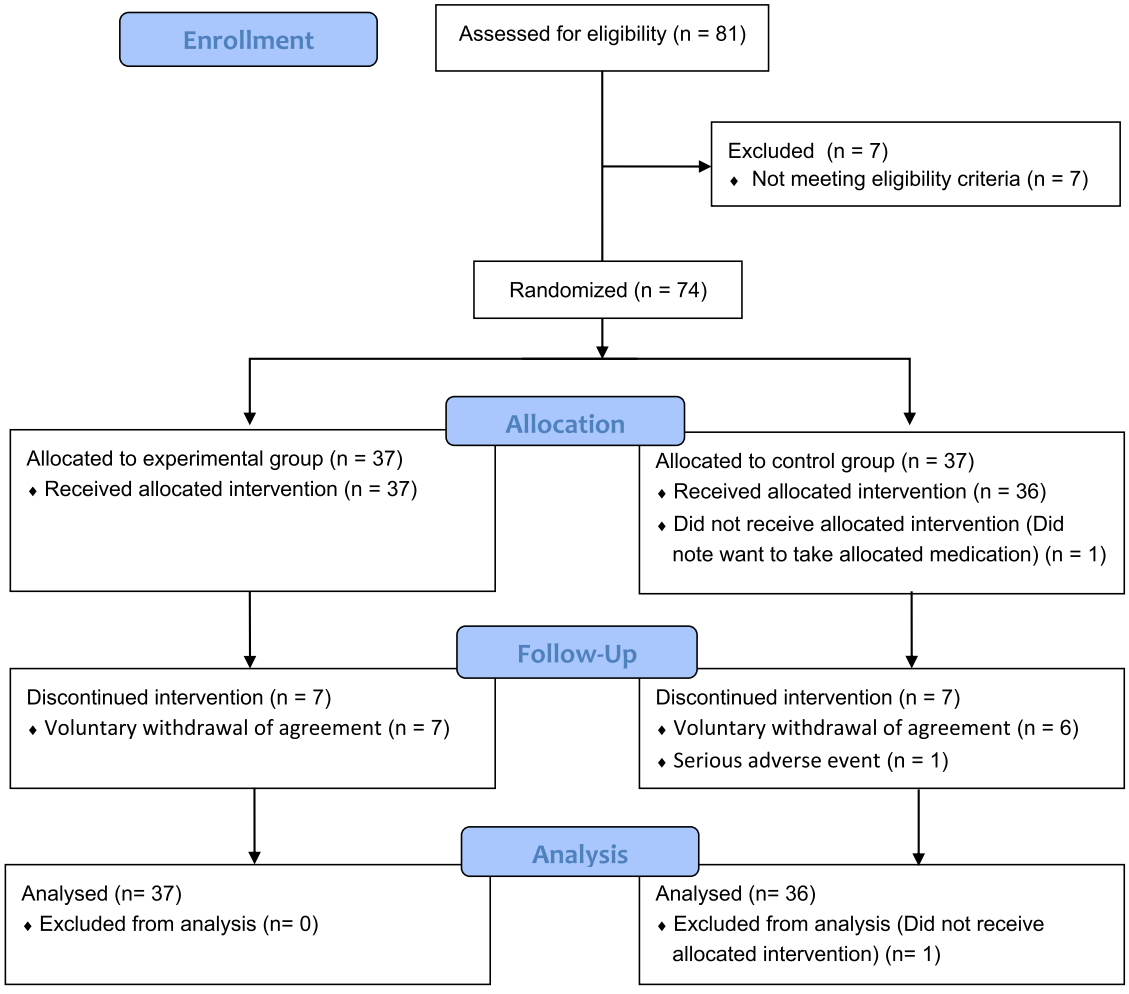

Fig. 1. Flow diagram.

Table 1
General characteristics at baseline.

Characteristics		Experimental group (n = 37)	Control group (n = 36)	p-value
Sex	Male	17	18	0.729
	Female	20	18	
Age	Years	50.6 ± 10.66	54.2 ± 8.58	0.120
Duration from onset	Months	144.5 ± 149.36	138.6 ± 120.79	0.856
Side of radiating pain	Right	14	16	0.785
	Left	16	15	
	Both	7	5	
Type of disc herniation	Bulging	20	13	0.548
	Protrusion	10	19	
	Extrusion	7	4	
	Sequestration	0	0	
Number of lesions	1 level	17	13	0.913
	2 levels	11	16	
	3 levels	5	5	
	4 levels	4	1	
	5 levels	0	1	
VAS for low back pain		61.5 ± 13.47	61.7 ± 14.07	0.949
VAS for radiating pain at baseline		59.6 ± 16.27	56.3 ± 17.30	0.402
Oswestry disability index		37.2 ± 10.69	34.9 ± 11.72	0.379
Roland Morris disability questionnaire		9.0 ± 4.63	8.2 ± 4.31	0.436
Euro-Qol index		0.662±0.1324	0.664±0.1411	0.949
Euro-Qol VAS		53.6 ± 13.65	57.5 ± 16.54	0.278
Deficiency syndrome of kidney index		7.5 ± 3.63	8.4 ± 4.02	0.303

Categorical variables were presented as numbers and compared using the chi-square test. Continuous variables were presented as mean ± standardized deviation and compared using an independent t-test.
VAS, visual analogue scale.

type of disc herniation, and number of lesions, and in the baseline values of the outcome measurements (Table 1).

3.2. Primary outcome

3.2.1. Change of low back pain at the primary endpoint

The VAS for low back pain in the experimental group before treatment was 61.5 ± 13.5, significantly decreasing to 45.6 ± 22.3 after six weeks. ($p < 0.05$) In the control group, it was 61.7 ± 14.1 before treatment and significantly decreased to 45.6 ± 20.4 after six weeks. ($p < 0.05$) The VAS change in the experimental group was 15.9 ± 20.3 and 13.4 ± 17.4 in the control group (Table 2). The equivalence limit for the mean differences for VAS was set to 18, and the CI of the mean difference between groups at week 6 (95 % CI: −9.25, 8.37) was within the equivalence limit (Fig. 2).

3.3. Secondary outcomes

3.3.1. Equivalence test for low back pain after follow-up

In the experimental group, the VAS for back pain after ten weeks compared to before treatment significantly improved to 46.1 ± 23.7 ($p < 0.05$), and the change was 15.4 ± 22.7. In the control group, VAS also significantly improved to 46.8 ± 20.5 after follow-up ($p < 0.05$), and the change was 15.1 ± 16.8 (Table 2). The CI of the mean difference for low back pain at week 10 (95 % CI: −9.03, 9.62) was within the equivalence limit (Fig. 2).

3.3.2. Equivalence test for radiating pain

In the experimental group, the VAS for radiating pain at baseline was 59.6 ± 16.3 and significantly improved to 41.4 ± 26.0 and 41.2 ± 25.6 after 6 and 10 weeks, respectively, with changes of 18.2 ± 22.8 and

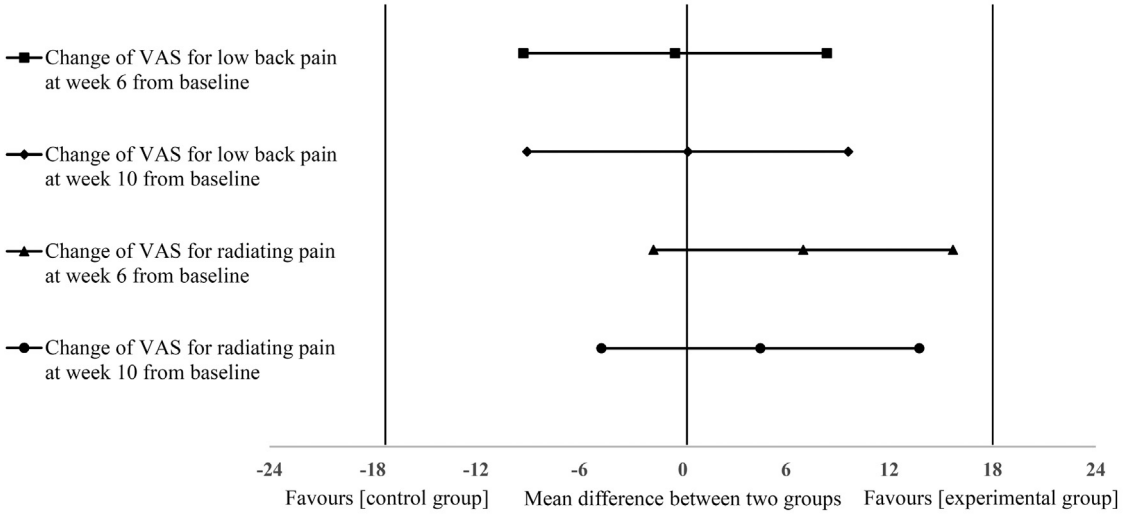

Fig. 2. Result of equivalence test for pain intensity. VAS, visual analogue scale.

Table 2
Comparison of changes in outcomes.

Group	Treatment period			Follow-up	p-value by RM-ANOVA
	Week 0	Week 3	Week 6	Week 10	
VAS for low back pain					
Experimental group	61.5 ± 13.5	54.1 ± 15.1*	45.6 ± 22.3*	46.1 ± 23.7*	0.992
Change from baseline		Δ7.4 ± 13.0	Δ15.9 ± 20.3	Δ15.4 ± 22.7	
Control group	61.7 ± 14.1	53.7 ± 16.4*	45.6 ± 20.4*	46.8 ± 20.5*	
Change from baseline		Δ8.3 ± 11.1	Δ13.4 ± 17.4	Δ15.1 ± 16.8	
p-value by independent *t*-test		0.752	0.921	0.950	
VAS for radiating pain					
Experimental group	59.6 ± 16.3	49.8 ± 21.1*	41.4 ± 26.0*	41.2 ± 25.6*	0.203
Change from baseline		Δ9.8 ± 16.1	Δ18.2 ± 22.8	Δ18.4 ± 22.4	
Control group	56.3 ± 17.3	50.3 ± 18.8*	45.7 ± 20.1*	42.9 ± 22.7*	
Change from baseline		Δ6.5 ± 11.2	Δ11.2 ± 13.0	Δ13.9 ± 16.7	
p-value by independent *t*-test		0.313	0.113	0.333	
Oswestry disability index					
Experimental group	37.2 ± 10.7	32.4 ± 11.8*	28.9 ± 12.8*	28.7 ± 14.3*	0.876
Change from baseline		Δ4.8 ± 6.3	Δ8.3 ± 7.9	Δ8.5 ± 11.3	
Control group	34.9 ± 11.7	31.5 ± 12.7*	27.5 ± 14.0*	26.5 ± 12.3*	
Change from baseline		Δ3.0 ± 7.9	Δ7.0 ± 9.0	Δ8.0 ± 8.3	
p-value by independent *t*-test		0.279	0.497	0.817	
Roland Morris disability questionnaire					
Experimental group	9.0 ± 4.6	7.5 ± 3.9*	7.2 ± 4.4*	6.9 ± 4.7*	0.667
Change from baseline		Δ1.5 ± 2.9	Δ1.8 ± 3.7	Δ2.1 ± 4.2	
Control group	7.9 ± 4.5	7.2 ± 4.6*	6.5 ± 4.7*	6.4 ± 4.8*	
Change from baseline		Δ0.8 ± 2.0	Δ1.4 ± 2.4	Δ1.6 ± 2.8	
p-value by independent *t*-test		0.173	0.569	0.550	
EQ-index					
Experimental group	0.662±0.132	0.699±0.122*	0.715±0.127*	0.729±0.130*	0.831
Change from baseline		Δ0.037±0.105	Δ0.037±0.105	Δ0.037±0.105	
Control group	0.664±0.141	0.699±0.118*	0.734±0.124*	0.728±0.106*	
Change from baseline		Δ0.035±0.074	Δ0.070±0.106	Δ0.064±0.123	
p-value by independent *t*-test		0.948	0.534	0.916	
EQ-VAS					
Experimental group	53.6 ± 13.6	56.4 ± 14.9	59.5 ± 20.0	63.7 ± 19.0*	0.477
Change from baseline		Δ2.8 ± 12.4	Δ5.9 ± 20.4	Δ10.1 ± 19.7	
Control group	57.5 ± 16.5	61.7 ± 16.9	63.3 ± 19.7	62.6 ± 15.9	
Change from baseline		Δ4.2 ± 16.1	Δ5.8 ± 24.5	Δ5.1 ± 20.9	
p-value by independent *t*-test		0.664	0.991	0.299	

The change from baseline of each outcome was compared using an independent *t*-test. The interaction between treatment and time was analyzed by RM-ANOVA.
RM-ANOVA, repeated measures analysis of variance; VAS, visual analogue scale.
* $p < 0.05$ by paired *t*-test for change before and after treatment within each group.

18.4 ± 22.4. In the control group, the VAS for radiating pain at baseline was 50.3, and it significantly improved to 45.7 and 42.9 after 6 and 10 weeks, respectively, with changes of 11.2 and 13.9 (Table 2). The CIs of the mean difference for radiating pain at week 6 (95 % CI: −1.70, 15.69) and week 10 (95 % CI: −4.72, 13.75) were within the equivalence limit (Fig. 2).

3.3.3. Comparison of function and quality of life

When analyzing changes within the group, both groups showed significant improvement in ODI, RMDQ, and EQ-index after treatment compared to before treatment. However, in EQ-VAS, only the experimental group showed significant improvement at week 10, and there was no significant change in the control group. There were no significant differences when comparing the change between groups for all outcome measures (Table 2 and Fig. 3).

3.3.4. Global perceived effect

The results of GPE, which evaluated subjective changes after treatment, were presented in Table 3. There were no significant differences between the two groups.

3.4. Adverse events

Ten cases of AEs occurred in the experimental group and 10 in the control group. There were two serious AEs, one in the experimental group and one in the control group. Serious AEs occurred due to traffic accidents and traumatic disc ruptures and were not related to the interventions of the trial. Traffic accidents occurred during the follow-up period and did not affect the intervention.

When estimating the relationship between AEs and interventions, one case of mild itching and one case of heartburn could be related to the intervention of the experimental group. Rhinitis, neck pain, dry eyes, shoulder pain, and sore throat were also observed in the experimental group, but it was judged that the relationship with the intervention was not high. In contrast, seven cases of heartburn that were assumed to be highly related to interventions occurred in the control group. It was judged that the tinnitus and dizziness in the control group were unlikely to be related to the intervention.

After treatment, the results of laboratory tests, including liver and renal function tests, were within the normal range in both groups.

4. Discussion

Comparing the effectiveness of UCSGH and loxoprofen through an RCT on patients with LHIVD showed a similar level of pain reduction within the equivalence range in low back and radiating pain. In addition, outcome measures for function and QoL also showed improvement at a level with no statistical difference.

Several RCT studies have reported that NSAIDs were significantly effective in reducing the pain intensity of back pain and sciatica.[19–22]

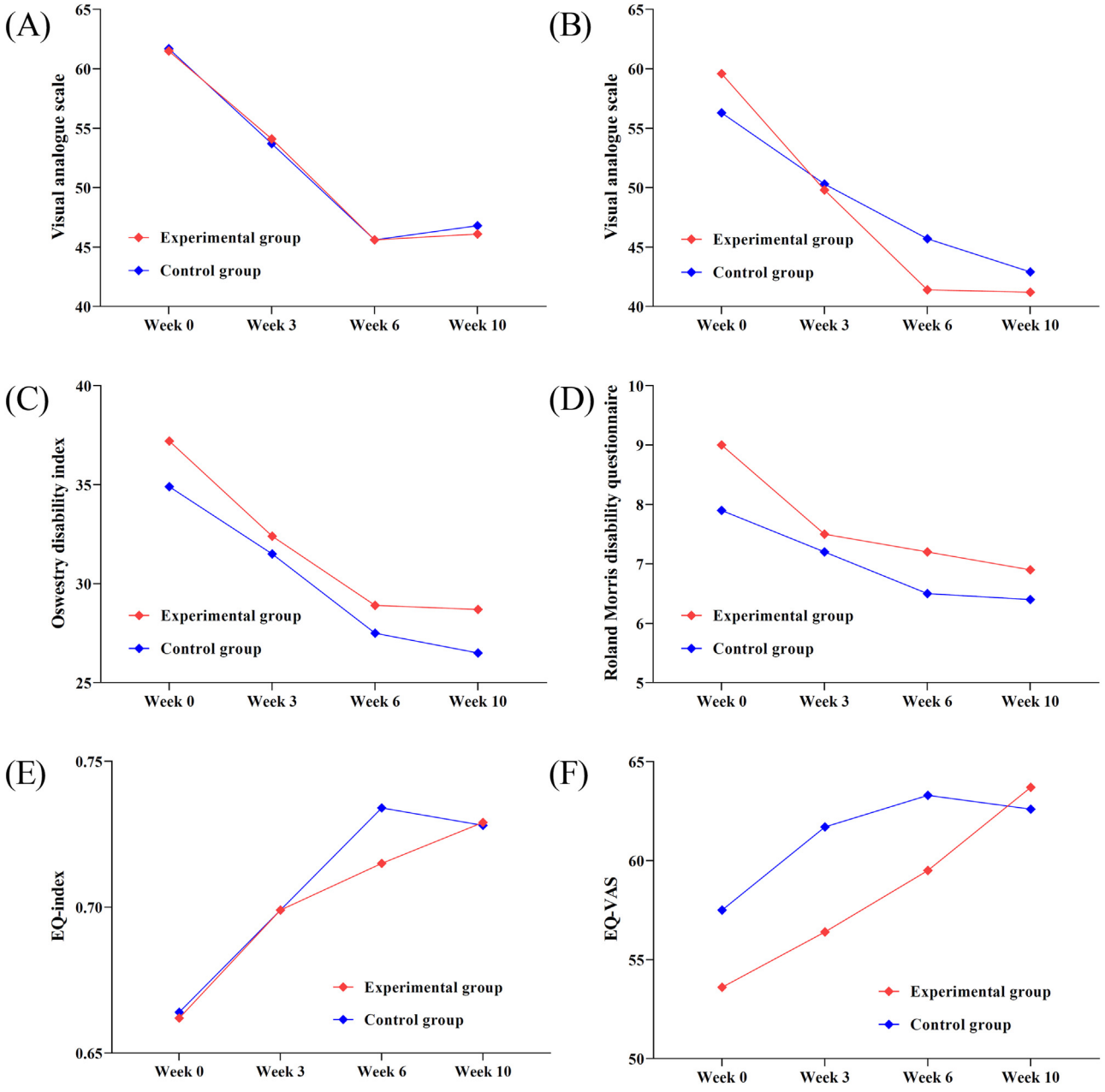

Fig. 3. Change in outcomes over time. VAS, visual analogue scale.

Table 3
Global perceived effect.

Global perceived effect	Week 6		Week 10	
	Experimental group (n = 37)	Control group (n = 36)	Experimental group (n = 37)	Control group (n = 36)
Worst ever	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
Much worse	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
Worse	0 (0 %)	1 (2.8 %)	2 (5.4 %)	0 (0 %)
Not improved and not worse	14 (37.8 %)	10 (27.8 %)	15 (40.5 %)	15 (41.7 %)
Slightly improved	14 (37.8 %)	17 (47.2 %)	12 (32.4 %)	16 (44.4 %)
Much improved	9 (24.3 %)	8 (22.2 %)	6 (16.2 %)	5 (13.9 %)
Best ever	0 (0 %)	0 (0 %)	2 (5.4 %)	0 (0 %)
p-value	0.804		0.958	

Therefore, although the systematic literature reviews could not reach a clear conclusion about the effect of NSAIDs due to the low level of evidence or small effect size,[23–25] NSAIDs used as control interventions are the primary option in the conservative medical treatment of spinal pain disorders.[26] Therefore, in this study, NSAIDs, which are most frequently used clinically, were set as the control for comparison. Acupuncture treatment was used concurrently, similar to the treatment pattern in actual clinical settings in Korea, because 91.4 % of traditional Korean medicine doctors responded that acupuncture was the most frequently used treatment method for LHIVD in our previous survey.[27]

UCSGH is a herbal medicine prescription consisting of the following 10 herbal medicines: *Rehmannia glutinosa, Achyranthes bidentata Blume, Cornus officinalis, Dioscorea batatas Decne, Plantago asiatica, Alisma orientale, Poria cocos, Paeonia suffruticosa, Cinnamomum cassia*, and *Aconitum carmichaelii*. The clinical effectiveness and mechanism of UCSGH can be explained based on studies on the individual herbal medicines that make up the prescription. *Aconitum* species, whose main ingredient is aconitine, has been used in traditional Korean medicine to treat severe pain and numbness. Through various modern experimental studies, the effect and mechanism of its analgesic effect on neuropathic pain are reported.[28–30] *Rehmannia glutinosa* and its effective component catapol showed anti-inflammatory effects,[31,32] and *Achyranthes bidentata* showed anti-inflammatory and neuroprotective effects.[33,34]

Based on the efficacy of these individual herbal medicines, UCSGH has been used for various pain diseases, such as diabetic neuropathy and chemotherapy-induced peripheral neuropathy.[35–37] The clinical effects of UCSGH in this study might be related to these mechanisms. Regarding safety, aconitine is known to have cardiotoxicity and neurotoxicity[38] and there is a lack of safety data on hepatotoxicity and nephrotoxicity for individual herbal prescriptions because herbal prescriptions consist of various herbal medicines with various components. In this study, blood tests showed no harm to liver and kidney function by UCSGH, and AEs related to UCSGH appeared at a lower frequency than the control group.

In this study, the equivalence margin of 18 suggested in a previous study was applied to confirm the equivalence of the two medications' effects on pain. In other studies, the non-inferiority margin was set at 8.39 for acute low back pain[39] and 5 for chronic low back pain.[40] If the results of this study are analyzed based on these more limited criteria, the significance of the results may change, so the results should be interpreted limitedly. Because the effects of UCSGH showed significant deviation between participants, it is necessary to establish criteria for selecting participants based on more precise indications to conduct further research to supplement this limitation. This trial was valuable in suggesting the possibility of herbal medicine treatment for LHIVD through comparison with conventional medication treatment. However, blinding of participants could not be achieved due to the difference in the form of granules and tablets. Because acupuncture treatment was used concurrently to reflect the treatment pattern in actual clinical settings, the influence of acupuncture treatment on the improvement after treatment cannot be ruled out.

In conclusion, UCSGH showed an equivalent level of effectiveness in reducing low back and radiating pain in patients with LHIVD compared to loxoprofen. The low incidence of AEs and normal laboratory test results in this trial suggest that UCSGH might be a safe treatment. These results provided evidence for using UCSGH as a conservative therapeutic option when treating patients with LHIVD.

CRediT authorship contribution statement

Bonhyuk Goo: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Visualization. **Jung-Hyun Kim:** Writing – review & editing. **Eun-Jung Kim:** Methodology, Investigation, Writing – review & editing. **Dongwoo Nam:** Methodology, Investigation, Writing – review & editing. **Hyun-Jong Lee:** Methodology, Investigation, Writing – review & editing. **Jae-Soo Kim:** Methodology, Investigation, Writing – review & editing. **Yeon-Cheol Park:** Writing – review & editing. **Yong-Hyeon Baek:** Writing – review & editing. **Sang-Soo Nam:** Writing – review & editing. **Byung-Kwan Seo:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

Funding

This study was supported by the Traditional Korean Medicine R&D program, which is funded by the Ministry of Health and Welfare through the Korea Health Industry Development Institute (KHIDI) (HB16C0061).

Ethical statement

The protocol of this study has been approved by the institutional review boards of four respective institutions (reference number: KHUHGD, KHNMCOH 2017–08–002; KHUMC, 170,918-HR-039; DUBOH, 2017–0007; and DKMHDHU, DHUMC-d-17,019). The informed consent form must be completed voluntarily before screening.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2024.101090.

Supplement 1. Composition of Uchashingihwan extract

Supplement 2. Details of acupuncture treatment using the STRICTA 2010 checklist

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