Complementary Therapies in Medicine (2010) **18**, 78—86

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Integrative package for low back pain with leg pain in Korea: A prospective cohort study☆

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Available online 13 April 2010

KEYWORDS
Low back pain;
Integrative medicine;
Disc herniation;
Acupuncture;
Herbal medicine;
Spinal manipulation

Summary Back pain significantly affects both patients and society through personal suffering, supporting burden, work loss, and incurred expenses. With no unequivocal support for surgery versus conservative treatment, an integrative approach has become popular in Korea.
Objectives: To investigate the outcomes of an integrative package for low back pain with leg pain.
Methods: A prospective cohort study involving patients with low back and leg pain and confirmed disc herniation was carried out at an outpatient clinic in Korea. The treatment package comprised of herbal medicines, acupuncture, bee venom acupuncture, and a Korean version of spinal manipulation (Chuna). Study participants were evaluated at baseline and every 4 weeks for 24 weeks. Low back and leg pain intensity levels were measured on a visual analog scale (0—10), back function was evaluated with the Oswestry Disability Index (0—100), and the overall quality of life was assessed using the SF-36 Health Survey (0—100 in 8 different subcategories).
Results: Out of 150 patients, 128 completed the 24 weeks of therapy. Patients reported improvements in all outcome measures. At the completion of the study, low back pain scores improved by a mean of 3.3 (95% CI = 2.8 to 3.8), and leg pain scores improved by a mean of 6.3 (95% CI = 5.9 to 6.6). Significant improvements in ODI and SF-36 scores were observed at 4 weeks and sustained throughout.
Conclusions: This integrative package was effective in the treatment of LBP with leg pain and warrants further rigorous investigations.

Introduction

Low back pain (LBP) affects both patients and society in many ways including personal suffering, reduced productivity, lost workdays, and financial costs. An American analysis reported individuals with work-related cases of back pain

☆ Sources of support: This study was funded by the Jaseng Medical Foundation, Seoul, Korea and by the Korean Science and Engineering Foundation, Daejeon, Korea.
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doi:10.1016/j.ctim.2010.02.003

lost 101.8 million workdays[1] in 1 year. The magnitude of this disorder is similar in South Korea where, in 1997, the compensation database for work-related LBP ($n = 9277$) showed the mean duration of back pain treatment is 252.6 days, and mean cost of total insurance benefit is around $37,700 USD equivalent.[2]

While LBP tends to improve over time, for many people it becomes chronic, requiring various interventions. Surgery can be effective where there is a clearly identified structural pathology that is likely to be the cause of the pain[3,4] however, chronic LBP may exist without the presence of an identifiable structural pathology.[4,5] Conversely, resolution of a structural pathology does not always resolve LBP.[6] Taking into account the costs, risks, and discomforts associated with surgery and the uncertain results, surgery is often considered a treatment of last resort for LBP.[4]

Non-operative treatments for LBP include a wide range of approaches. In a systematic review, van Tulder[7] concluded that active approaches to LBP patients involving NSAIDs, muscle relaxants, exercise therapy, back schools (educational and skills acquisition programs for patients with LBP),[12] and behavioral therapy were effective. Several recent systematic reviews lend support to the use of acupuncture,[8–10] exercise therapy,[11] back schools,[12] behavioral treatment,[13] and spinal manipulative therapy.[14] Evidence-based reviews covering non-invasive treatments[15] or non-pharmacologic therapies[5] for LBP further supported spinal manipulative therapy and acupuncture. However, while each therapeutic approach has its own time window, there is no single therapy that is unequivocally successful, hence multi-modality approaches are often sought and practiced.

In South Korea, the traditional system of medicine has evolved into a more integrative system since the introduction of Western medicine in 1907.[16] Significant numbers of patients seek non-surgical conservative treatment at clinics where both modern diagnostic procedures and integrative treatments are available. For LBP, a standard clinical care model has evolved to include herbal medicine,[17] spinal manipulation,[18,19] bee venom acupuncture,[20] and acupuncture.[10,21] This is the report of a prospective cohort study that received 6 months of treatment for LBP with leg pain. While we discuss the findings on clinical outcomes, we also evaluate a number of factors that might correlate to the outcomes.

Methods

Participants

The study was approved by institutional review boards (IRB) of both the University of North Carolina at Chapel Hill and the Jaseng Hospital in Korea due to the nature of the international collaboration. The study was conducted at Jaseng Hospital in Korea, which offers both Western and Korean medical services. Patients who were recruited for the study had not been previously treated for LBP at this hospital. Some were referred with lumbar disc herniation already confirmed by MRI. Others were self-referred and their lumbar disc herniation was confirmed with MRI once admitted. Moreover, all patients included presented serious conditions through their history or physical examination. This initial diagnosis conforms to the Clinical Practice Guideline jointly issued by the American College of Physicians and the American Pain Society.[22]

Patients meeting the following criteria were included: (1) LBP with leg pain, of which pain level is 4 or higher in VAS with post-onset within a year; (2) lumbar disc herniation confirmed by MRI; and (3) age between 18 and 60. The exclusion criteria were: (1) back pain caused by non-spinal or soft tissue problems, e.g. pregnancy, spinal tumor, and rheumatoid arthritis; (2) VAS of pain 4 or less; (3) history of back surgery, vertebral fracture, dislocation, or cancer; (4) suspected concurrent severe neurological symptoms, such as *cauda equina* syndrome; (5) suspected pregnancy; (6) unexplained weight loss; and (7) major organ transplantation (such as heart, kidney, or liver).

Interventions

The therapeutic package, allowing some individual tailoring at physician's discretion, consisted of weekly treatments and daily intake of herbal medicine for 24 weeks. They included: (1) 20 min sessions of acupuncture[10,21]; (2) 20 min sessions of a Korean version of spinal manipulation known as Chuna[24] (a treatment that includes conventionally defined spinal manipulation,[18,19] an application of high-velocity, low amplitude thrusts to the spinal joints slightly beyond the passive range of joint motion and spinal mobilization, an application of manual force to the spinal joints within the passive range of joint motion that does not involve a thrust); (3) bee venom acupuncture[20] (apitoxin subcutaneous injection on acupoints) at physician's discretion; (4) a capsule containing *Cibotium barometz* and *Atractylodes japonica* in dry powder form (2 g), twice daily; and (5) water extracted decoction (120 ml) of herbal prescription as prescribed by attending physicians from the 10 herbal medicines listed below, twice a day, 30 min after meal.

The 10 herbal medicines are Ostericum koreanum, Eucommia ulmoides, Acanthopanax Sessiliflorus, Achyranthes bidentata, Psoralea corylifolia, Peucedanum japonicum, Cibotium barometz, Lycium chinense, Boschniakia rossica, and Cuscuta chinensis. The above herbal medicines in powder and decoction forms are well noted in traditional Chinese and Korean medicine for treatment of low back pain[17] and are part of the historically developed treatment practiced at Jaseng Hospital.[23] Moreover, recent scientific investigations reported the compounds of Cibotium barometz showed inhibition of osteoclast formation in vitro,[24] and the extract of Atractylodes japonica protects osteoblast cells from oxidative stress.[25] The powder forms of these two herbs have been empirically used to diminish damp conditions of the body to help low back pain. For the herbal decoction, Eucommia ulmoides has been reported to have osteoblast-like cell proliferation, osteoclast inhibition effects[26] and improve bone biomechanical quality through modifications of bone mineral density.[27] While treatment period for chronic LBP in clinical practice may vary, we chose 24 weeks to maximize the observational period.

Outcome measures

Primary outcome measure was visual analogue scale[28] (VAS, 0—10) of back pain and leg pain, while the Oswestry Disability Index[29] (ODI) and SF-36 Health Related Quality of Life Questionnaire[30,31] were secondary. These were assessed at baseline, 4th, 8th, 12th, 16th, 20th, and 24th week.

Safety assessments

Any adverse event was monitored carefully; in particular, a full liver function test was carried out at baseline, and again at weeks 12 and 24 to identify any drug induced liver injury (DILI). This test included serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBR). In identification of DILI, for those with pre-treatment serum AST and ALT levels within normal range (AST, 35 U/L; ALT, 31 U/L; TBL, 1.4 U/L), we used Council for International Organizations of Medical Science criteria, which requires at least two determinations of ALT plasma concentrations above 2 ULN (upper limit of normal range) (criterion I), conjugated bilirubin above 2 ULN (criterion II), or combined increases of aspartate aminotransferase (AST), alkaline phosphatase (AP) and total bilirubin (tBili) with one value above 2 ULN (criterion III).[32]

Following the method used by Sulkowski et al.[33] those patients with elevated pre-treatment serum AST and ALT levels (higher than the upper limit of normal (ULN)) were classified based on changes relative to baseline rather than ULN: grade 0 (<1.25 × baseline); grade 1 (1.25—2.5 × baseline); grade 2 (2.6—3.5 × baseline); grade 3 (3.6—5 × baseline); and grade 4 (>5 × baseline). Changes in serum TBR were classified based on changes relative to ULN: grade 0 (>1.1 × ULN); grade 1 (1.1—1.5 × ULN); grade 2 (1.6—2.9 × ULN); grade 3 (3—5 × ULN); and grade 4 (>5 × ULN).

Statistical analysis

Descriptive analyses were performed for all data using SPSS software for Windows (Version 12.0, SPSS Corp., Chicago, IL, USA). A confirmatory analysis of a single primary outcome was not intended for this study. Instead, changes from baseline for outcome measures of major interest were presented as mean differences with the 95% confidence interval.

Testing for differences in outcomes among predefined subgroups and interactions between time (baseline, 4th, 8th, 12th, and 24th weeks) and subgroups was performed by repeated measures two factor analyses. For predefined subgroups, the patients were divided into protrusion, extrusion, and both protrusion and extrusion groups[34] based on their initial MRI findings; acute (<4 weeks), sub-acute (4—12 weeks), and chronic (>12 weeks) groups[4] based on their onset of LBP or leg pain, whichever was earlier; operation recommended or not by surgeon at baseline[35]; underweight (BMI < 18.5), normal (18.5—23), overweight (23—25) and obese (>25) groups[36,37] based on their baseline BMI. Explorative correlation analysis was performed to investigate whether age was related with any of the outcomes including baseline LBP, leg pain, and ODI score at 12th and 24th week.

Estimates of a minimal clinically important change (MCIC) in mean VAS for chronic low back pain have been in the range of 20—35 mm[13,20] on VAS 1-100. For this study, a change in mean VAS from baseline of 30 mm (or 3.00 on VAS 1-10) was defined as MCIC[38,39] in both low back and leg pain. The MCIC in mean ODI has been estimated at 10 points.[13]

Results

Patients

From November 2006 to October 2007, 4184 patients were screened and a total of 150 patients were included in the study. Of the 4034 patients who failed screening, the majority had LBP caused by non-spinal or soft tissue problems (2124) or VAS of pain 4 or less (1599).

Of the 150 patients who were enrolled in the study, 116 suffered from sub-acute or chronic LBP, while 34 experienced acute LBP. 128 of the 150 patients completed the 6-month treatment (Fig. 1). The reasons for drop out ($n = 22$) include undergoing surgical operation ($n = 8$); dissatisfaction with the treatment ($n = 3$); symptom improvement immediately after entering into the study ($n = 2$); losing contacts ($n = 3$); and changes in personal circumstances ($n = 6$). Patient characteristics and baseline values are presented in Table 1. There was no significant difference in BMI between baseline and 6 months ($n = 127$, paired t-test, $p = 0.319$).

Table 1 Baseline characteristics of study participants ($n = 150$).

Characteristic	% (n)	Mean (SD)
Proportion of males	58.7 (88)	
Age (years)		34.7 (8.4)
Proportion with herniated disc		
Protrusion	57.4 (86)	
Extrusion	17.3 (26)	
Both	14.0 (21)	
Other	11.3 (17)	
Proportion with duration of low back pain		
<4 weeks (acute)	22.7 (34)	
4—12 weeks (sub-acute)	42.0 (63)	
>4 weeks (chronic)	35.3 (53)	
Proportion with recommended surgery[a]	61.3 (92)	
Body mass index		23.9 (2.8)
Proportion with BMI		
Underweight	1.3 (2)	
Normal	42.0 (63)	
Overweight	24.7 (37)	
Obese	32.0 (48)	

[a] Surgery recommended by surgeons consulted prior to participation in the study.

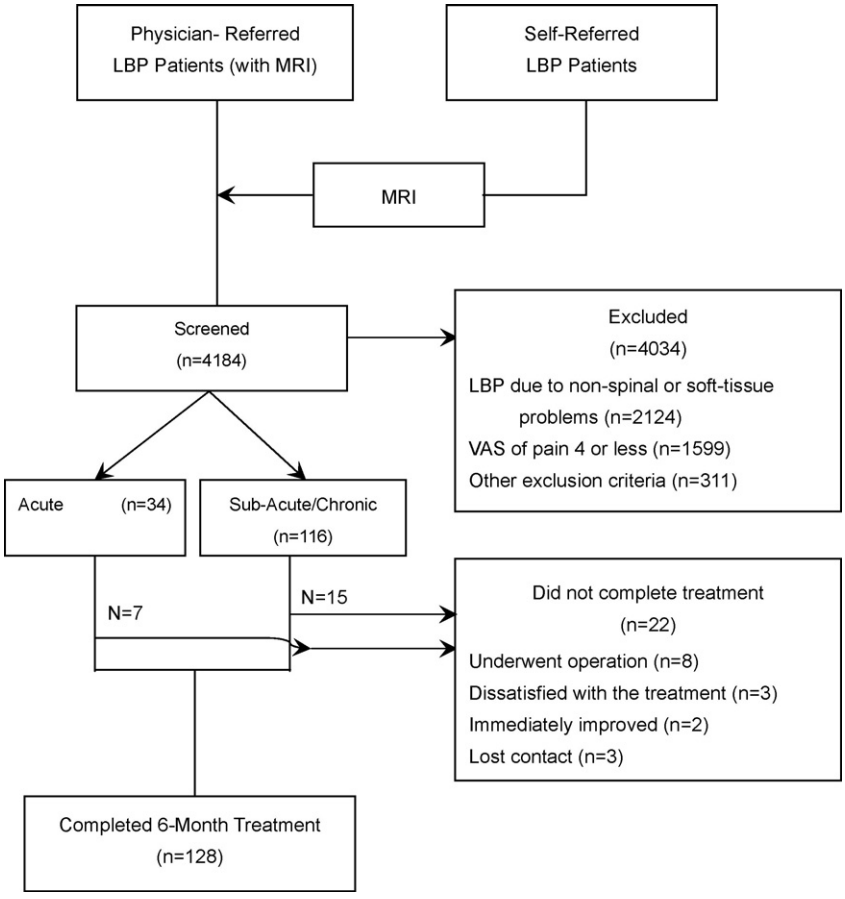

Figure 1 Flow diagram of the study.

Compliance

As is often observed in clinical practice, compliance decreased gradually over time. Of the 150 patients enrolled at baseline, 142 returned at 4 weeks, 134 at 8 weeks, 131 at 12 weeks, and 128 returned for the final treatment session at 24 weeks (Fig. 1).

Outcomes

Symptoms of LBP and leg pain, and the level of disability significantly decreased from the 4th week, and continued to decrease to week 24. Six months after beginning treatment, patients reported significant improvements in all relevant outcome measures (Tables 2 and 3). VAS for leg pain, an average of 6.28 (95% CI [5.93 to 6.62]) points was

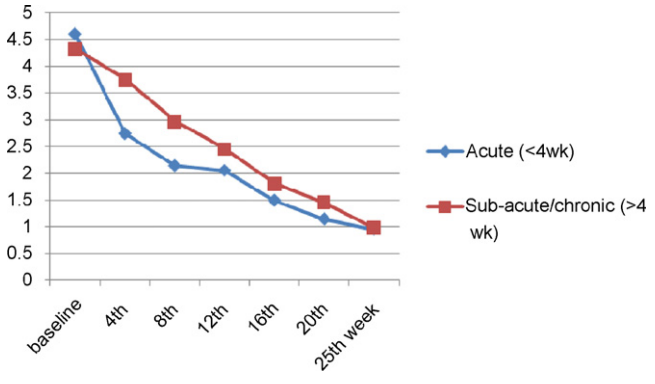

Figure 2 Changes of low back pain in VAS over time. Y axis: VAS of 1—10; X axis: time (week). 95% confidence of intervals of VASs of low back pain at 4th week are [1.99 to 3.49] and [3.3 to 4.17] for the acute LBP group and the sub-acute/chronic group, respectively. Those at 8th week are [1.57 to 2.71] and [2.57 to 3.36], respectively.

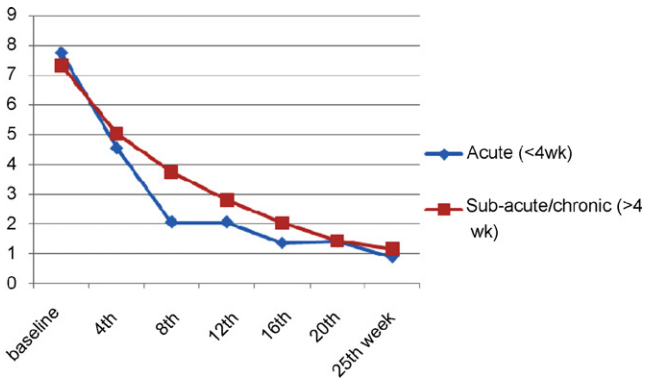

Figure 3 Changes of radicular pain in VAS over time. Y axis: VAS of 1—10; X axis: time (week). 95% confidence of intervals of VASs of radicular pain at 8th week are [1.76 to 3.18] and [3.31 to 4.15] for the acute LBP group and the sub-acute/chronic group, respectively.

Table 2 Changes in clinical outcome measures for all participants during the course of treatment.

	Baseline ($n = 150$)	4 weeks ($n = 142$)	8 weeks ($n = 134$)	12 weeks ($n = 131$)	24 weeks ($n = 128$)
Low back pain VAS score					
Mean (SD)	4.39 (2.73)	3.54 (2.35)	2.82 (2.01)	2.36 (1.95)	1.07 (1.27)
Mean change[a] (95% CI)		0.85 (0.42, 1.27)	1.44 (1.00, 1.88)	1.92 (1.42, 2.43)	3.29 (2.82, 3.77)[b]
Leg pain VAS score					
Mean (SD)	7.42 (1.36)	4.91 (2.23)	3.51 (2.18)	2.63 (2.11)	1.09 (1.55)
Mean change[a] (95% CI)		2.49 (2.09, 2.89)	3.88 (3.45, 4.31)[b]	4.73 (4.30, 5.16)[b]	6.28 (5.93, 6.62)[b]
Oswetry disability index					
Mean (SD)	41.4 (15.5)	33.7 (14.8)	25.9 (14.6)	21.1 (14.6)	11.8 (11.2)
Mean change[a] (95% CI)		7.9 (5.6, 10.3)	15.4 (12.2, 18.6)[b]	22.1 (16.8, 23.4)[b]	29.3 (26.2, 32.5)[b]
SF-36 subscales physical functioning					
Mean (SD)	40.8 (21.9)	51.6 (21.4)	62.0 (22.4)	67.0 (21.6)	82.7 (15.2)
Mean change (95% CI)		11.9 (15.9, 7.9)	22.3 (26.7, 18.0)	27.3 (31.8, 22.8)	42.9 (47.2, 38.6)
Role-physical					
Mean (SD)	13.8 (22.7)	21.1 (27.9)	28.4 (31.0)	38.9 (35.8)	61.1 (33.8)
Mean change[a] (95% CI)		8.2 (13.1, 3.2)	15.9 (21.2, 10.5)	26.2 (32.5, 19.8)	48.4 (54.8, 42.0)
Bodily pain					
Mean (SD)	26.5 (18.4)	42.0 (19.3)	48.6 (18.1)	53.2 (17.9)	66.2 (15.9)
Mean change[a] (95% CI)		16.0 (19.8, 12.2)	23.2 (27.1, 19.2)	27.7 (31.8, 23.6)	40.8 (44.9, 36.7)
General health					
Mean (SD)	51.8 (16.5)	53.4 (15.3)	54.4 (16.2)	55.5 (15.8)	58.3 (16.1)
Mean change[a] (95% CI)		2.6 (4.8, 0.4)	3.5 (5.9, 1.2)	4.8 (7.2, 2.5)	7.8 (10.4, 5.2)
Vitality					
Mean (SD)	38.2 (17.3)	44.1 (15.7)	48.4 (14.9)	50.4 (14.8)	57.3 (15.1)
Mean change[a] (95% CI)		7.2 (9.7, 4.8)	11.8 (14.6, 9.0)	14.4 (17.5, 11.4)	21.4 (24.7, 18.1)
Social functioning					
Mean (SD)	42.1 (18.8)	46.7 (17.1)	52.8 (17.0)	58.1 (19.7)	71.4 (17.8)
Mean change[a] (95% CI)		5.6 (9.1, 2.2)	12.7 (16.4, 9.0)	18.2 (22.6, 13.9)	31.6 (35.8, 27.5)
Role-emotional					
Mean (SD)	21.3 (34.6)	25.8 (37.5)	36.0 (42.3)	46.1 (43.8)	68.0 (41.1)
Mean change[a] (95% CI)		4.8 (11.5, 2.0)	16.2 (24.3, 8.0)	26.7 (35.1, 18.2)	47.9 (56.2, 39.6)
Mental health					
Mean (SD)	50.6 (16.8)	55.4 (15.4)	59.2 (14.8)	62.3 (13.8)	66.9 (14.3)
Mean change[a] (95% CI)		5.2 (7.5, 2.8)	9.3 (12.1, 6.6)	12.9 (16.0, 9.7)	17.5 (20.7, 14.3)

VAS, visual analog scale (0—10); CI, confidence interval.

[a] Mean difference from baseline.

[b] Exceeds the MCIC relative to baseline.

Table 3 Changes in mean low back pain VAS scores for categories of participants during the course of treatment.

	Baseline	4 weeks	8 weeks	12 weeks	24 weeks
Categories of LBP duration					
Acute: mean ± SD (*n*)	4.6 ± 2.8 (34)	2.7 ± 2.2 (29)	2.1 ± 1.7 (27)	2.0 ± 1.8 (27)	1.3 ± 1.7 (27)
Sub-acute: mean ± SD (*n*)	3.9 ± 2.6 (63)	3.3 ± 2.1 (63)	2.6 ± 1.8 (62)	2.1 ± 1.7 (60)	0.9 ± 0.8 (58)
Chronic: mean ± SD (*n*)	4.8 ± 2.8 (53)	4.3 ± 2.5 (50)	3.5 ± 2.3 (45)	2.9 ± 2.3 (44)	1.2 ± 1.4 (43)
Categories of LBP surgery recommendation					
Recommended: mean ± SD (*n*)	3.8 ± 2.6 (92)	3.4 ± 2.4 (87)	2.8 ± 2.0 (83)	2.3 ± 2.0 (80)	1.2 ± 1.3 (78)
Not recommended: mean ± SD (*n*)	5.3 ± 2.7 (58)	3.8 ± 2.3 (55)	2.8 ± 2.0 (51)	2.5 ± 2.0 (51)	0.9 ± 1.1 (50)

VAS, visual analog scale (0–10); LBP, low back pain.

reduced from the initial value of 7.42 on a 100 mm scale (Fig. 3). VAS for LBP improved at 6 months by 3.29 (95% CI [2.82 to 3.77]) from mean 4.39 at baseline (Fig. 2). In other variables including Oswestry Disability Index (ODI) and health related quality of life (SF-36), patients also showed significant improvement 1 month after the beginning of treatment. Improvement was sustained until the end of the 6-month treatment (Fig. 4).

Most of the study's population (77.3%) has suffered severe leg pain as well as LBP for mid long term (>4 weeks). Minimal clinically important change (MCIC) in VAS for LBP was met at 24 weeks and in VAS for leg pain at 8, 12, and 24 weeks. The MCIC in ODI at 8, 12, and 24 weeks were also met. In addition, although they chose to seek non-surgical treatment, about 61.3% ($n = 92$) of participants were once recommended for surgical operation, indicating the severity of their symptoms.

Regarding more detailed SF-36 subscale outcomes, continuous significant improvements were observed in all eight of the subscales. The magnitude of improvement was in the order of limitation of roles caused by physical function and emotion, physical functioning, bodily pain, social functioning, vitality, mental health, and general health (Table 2).

The trend of SF-36 subscale changes over the observational period may illustrate that (1) as body pain decreases and physical and social functioning improves, the limitations caused by physical function and emotion decreases, and (2) vitality and mental health improve. While this trend is similar to other findings measuring the same SF-36 measure, the magnitude of the change in this study is meaningful.

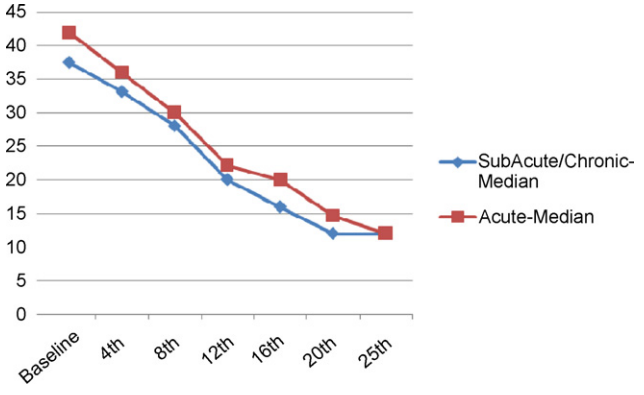

Figure 4 Changes of low back pain related Oswestry Disability Index over time.

Subgroup analyses

The study had 4 predefined subgroups: MRI findings, duration of disease, recommendation for operation, and BMI. In subgrouping by the duration of LBP, moderate group difference ($F = 4.104$, $p = 0.019$) and time by group interaction difference ($F = 2.326$, $p = 0.024$) were found in VAS for LBP; and so was time by group interaction difference in ODI score ($F = 2.612$, $p = 0.018$). This may indicate different healing patterns over time among the subgroups. In subgroups organized by operation recommendation, there were significant time by group interactions for VAS for LBP ($F = 2.626$, $p = 0.039$), which could mainly be explained by the baseline difference, i.e. the baseline VAS for LBP of those who self-referred without consulting surgeons was higher than those who have (Table 5).

In summary, acute patients significantly improved within 4 weeks, while the patients in the other groups took longer, and the magnitude of improvement was slowest in the chronic group. Those who were recommended for receiving an operation show slower recovery than those who were not recommended despite having higher VAS pain scale scores.

However, considering the number of multiple comparisons, the interpretation of this subgroup analysis requires caution. Neither group difference nor time by group interactions was found in any other outcomes (Table 4). We found no other predefined factors including age, baseline leg pain, and SF-36 total score, significantly affected the main outcomes at either 12th or 24th week. In addition, the exact extent of structural deformity is difficult to establish since the recommendations for surgery were made by various surgeons.

Safety profile

Two patients who continued drinking alcohol with elevated aspartate aminotransferase and alanine aminotransferase were identified and advised to stop. One case of allergic reaction to bee venom acupuncture was identified within 30 min presenting rash, dizziness, and headache, and treated with anti-histamine. The symptoms disappeared within 10 h, and the patient continued treatment except this intervention. The liver function test results revealed that (1) pre-treatment levels of 82 patients (64%) were within normal range; (2) the elevated levels very often came down during the treatment period, with a few cases showing that levels were mildly elevated. Using both DILI criteria for

Table 4 Changes in mean Oswestry Disability Index for categories of participants during the course of treatment.

	Baseline	4 weeks	8 weeks	12 weeks	24 weeks
Categories of LBP duration					
Acute: mean ± SD (*n*)	46.6 ± 18.3 (34)	35.9 ± 16.0 (29)	19.6 ± 12.6 (27)	16.2 ± 14.0 (27)	11.6 ± 13.3 (27)
Sub-acute: mean ± SD (*n*)	41.5 ± 15.5 (63)	33.5 ± 14.6 (63)	26.5 ± 14.6 (62)	21.3 ± 13.0 (60)	11.0 ± 9.0 (58)
Chronic: mean ± SD (*n*)	37.9 ± 12.6 (53)	32.7 ± 14.4 (50)	28.8 ± 14.9 (45)	23.6 ± 16.6 (44)	13.1 ± 12.5 (43)
Categories of LBP surgery recommendation					
Recommended: mean ± SD (*n*)	41.6 ± 14.9 (92)	33.6 ± 14.7 (87)	26.1 ± 14.6 (83)	21.3 ± 15.1 (80)	13.4 ± 11.7 (78)
Not recommended: mean ± SD (*n*)	41.0 ± 16.6 (58)	33.9 ± 15.0 (55)	25.5 ± 14.8 (51)	20.8 ± 14.0 (51)	9.4 ± 10.0 (50)

ODI, Oswestry Disability Index (0—100); LBP, low back pain.

Table 5 Results from repeated measures two factor analysis of variance.

Categories	Scores	Group differences		Time by groups interactions	
		F test	*P* value	*F* test	*P* value
Disc herniation	LB pain VAS score	0.197	0.821	1.017	0.419
	Leg pain VAS score	0.061	0.941	1.237	0.275
	ODI score	0.627	0.536	1.338	0.240
Low back pain duration	LB pain VAS score	4.104	0.019	2.326	0.024
	Leg pain VAS score	2.417	0.093	1.620	0.115
	ODI score	0.144	0.866	2.612	0.018
LB surgery recommendation	LB pain VAS score	0.657	0.419	2.626	0.039
	Leg pain VAS score	0.552	0.459	0.406	0.806
	ODI score	0.347	0.557	0.624	0.598
Body mass index	LB pain VAS score	0.162	0.921	0.908	0.530
	Leg pain VAS score	1.765	0.157	0.944	0.503
	ODI score	0.905	0.441	1.163	0.318

LB, lower back; VAS, visual analog scale (0—10); ODI, Oswestry Disability Index (0—100).

normal and elevated pre-treatment levels, no DILI was identified.

Discussion

Key findings of this prospective observational study are (1) the total package of treatments were well tolerated with no significant adverse event requiring hospitalization, and with cautious application of bee venom acupuncture, and a professional response plan in place, the treatment package is safe; (2) the extent of LBP and leg pain, as well as the level of disability, significantly reduced from the 4th week, and continued to decrease to week 24; (3) health related quality of life measured by SF-36 significantly increased from the first month and continued to improve; (4) duration of LBP and whether or not surgical operation was recommended was moderately associated with the clinical outcomes.

This study exhibited several strengths: (1) the long observational period of 6 months allowed investigators to predict progress of treatment outcomes; (2) the combined approach is similar to real-world settings and the data collected can be informative for clinical environments; and (3) a high patient compliance rate. Considering that this study required an intense regiment of 24 visits, daily medicines and weekly spinal manipulation, a compliance rate of 85.3% (128 out of 150) indicates that the patients were highly satisfied, and the fact that no DILI was identified implies high tolerability and the safety of treatments. It is notable that the safety data from the package of treatments including more than 3072 sessions of spinal manipulation (24 sessions per patient multiplied by 128 patients completing total sessions), and agrees with the recent study suggesting that the risks of serious adverse events be considered negligible.[40]

However, there were also weaknesses: perhaps the most significant limitation is the nature of a prospective cohort study wherein we cannot make any definitive conclusions regarding treatment efficacy. Due to the lack of a control group, this study was unable to affirmatively comment on the effectiveness of individual treatment modalities or on the comparative effectiveness of an integrative package to conventional medical regiments. Additionally, considering the number of diverse factors involved in this study including the duration of suffering, existence of structural deformation, and sample size, this study should only serve the purpose of diligently describing the outcomes of this treatment package. Finally, multiple interventions, while pragmatic, make it difficult to attribute any effect to a spe-

cific ingredient. Several guidelines are now available on the development, evaluation and implementation of complex interventions,[41,42] which is the very format of the combined package approach of this study. Nonetheless, we regret that this is study is far from fully complying with the guidelines. Developing a complex intervention requires long preparation involving the identification of modalities, all of which have a coherent theoretical basis and evidence-based effectiveness. The combined package in this study was empirically developed without the above described process, and its feasibility was only established by trial and error. Hopefully, the outcome of this study will influence the development process of such a complex intervention.[43,44]

Despite these limitations, findings in this study compliment previous literature on LBP treatment. Since there is no unequivocal support of surgery[3,6] versus conventional treatment,[40,45] a patients' search for alternatives is justifiable. A randomized trial comparing medication, spinal manipulation and acupuncture indicated the beneficial use of their combination.[46] The package approach in this study becomes even more optimistic when considering the incorporation of bee venom acupuncture, which can be interpreted as a prolotherapy, i.e. repeated injections of an irritant solution to strengthen lumbosacral ligaments and reduce some types of chronic back pain. The conclusion of a cochrane review of prolotherapy for LBP supports our combined use.[47]

To conclude, this study is one of the few to thoroughly document interventions and outcomes of LBP patients receiving an integrative treatment package and certainly one of the only studies of Korea. The safety data collected from this prospective cohort support the continuation of such treatments, and the outcome data indicate the improvement of LBP in several aspects. We suggest a stepwise controlled study to address: (1) whether this package approach is more effective than other treatments; and (2) which treatment components of the package are more substantial than others. In summary, this integrative package was effective in the treatment of LBP with leg pain and warrants further rigorous investigations.

Conflict of interest

Drs. Joonshik Shin, Youngkwon Choi, Yousuk Youn, Sangho Lee, Seung-Ro Kwon, Man-Ho Kang, and In-Hyuk Ha were employees of the Jaseng Hospital during the period of the study. Otherwise, there is no other conflict of interest to declare.

Acknowledgements

This study was funded by the Jaseng Medical foundation, and Jongbae Park and Hyangsook Lee was supported by SRC program of KOSEF (R11-2005-014), and received consultation fee from the Jaseng Medical Foundation for carrying out the study. The authors thank Mr. Jaehong Kim for his administrative dedication to the implementation of the study, and Stephen Flaherty, Catherine Champagne, Julie Omohundro and Margeaux Akazawa for their assistance in manuscript preparation.

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