Skew-symmetric Random Effect Models with Application to a Preventive Cohort Study: Improving Outcomes in Low Back Pain Patients

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ABSTRACT

Background: To investigate the respective contribution of various biologic and psychosocial factors, especially Health Related Quality of Life (HRQOL) as a main outcome, in the natural history of acute low back pain (LBP) and to evaluate the impact of this condition on HRQOL.

Methods: In a prospective cohort study For 24 weeks, 150 patients were assessed at an outpatient clinic in Korea consulting for low back and confirmed disc herniation duration at inclusion and treated with 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 intensity levels were measured on a visual analog scale (0‑10), back function was evaluated with the Oswestry Disability Index (0‑100), disability assessed by HRQOL assessed by the short form 36 health survey (0‑100 in 8 different sub-categories).

Results: Out of 150 patients, 128 completed the 24 weeks of traditional therapy. Patients reported improvements SF-36 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). According to the results of our modeling, low back intensity level, back function and BMI measures had significant effects on quality of life during study. Interpreting the coefficients of modeling, the impact of the decreasing acute LBP episode on HRQOL by VAS and ODI outcomes, was high and important.

Conclusions: This study highlights the large contribution of integrative package therapy as an effective preventive method for improving LBP patient’s HRQOL.

Keywords: Low back pain, health related quality of life, oswestry disability index

INTRODUCTION

Low back pain (LBP) which has risen in most industrialized countries is one of the most frequent reasons both, for consulting a primary care physician and for taking time off
routine activities.\cite{1} Long term sickness absence, is associated with serious health risks, and future serious illness.\cite{2} Low back pain disorder affects 80% of the population at some time of their life,\cite{3} and corresponding costs led to important researches, concerning determinants, preventive exercises, and treatments.\cite{4} Studies showed that, having previous history of LBP is often prognostic of future back problems.\cite{5} Chronic cases of this problem which represent decreased muscle flexibility and trunk strength led to significant burden on the health care and compensation systems.\cite{6}

Perhaps, prevention of LBP in primary stages, contribute to prevention of disabilities of back pain in progressive stages.\cite{7,8}

Some indicative health instrument would be useful to explore health related quality of life (HRQOL) in relation to LBP.\cite{9,10} HRQOL measurement instruments have been developed to evaluate health status and its components, such as physical activity, psychological functioning (emotional and mental activity), social functioning (relationships with others and participation in social activities), perception of health status, and pain.\cite{11} These measurements have been widely used to evaluate the broad impact of various diseases on patients and the effectiveness of different conditions and also to be related to the extent of satisfaction with care associated with various treatments.\cite{11} The documentation of factors predictive of a developed impact of LBP on HRQOL would be of great value for defining management strategies.\cite{12}

Although LBP tends to increase over time, for many people it becomes chronic, requiring different interventions. Surgery can be effective where there is a clearly recognized structural pathology that is possible to be the cause of the pain\cite{13} but, chronic LBP may exist without having an identifiable structural pathology.

Considering the costs, risks and distresses associated with surgery methods and the indistinct results, surgery is often considered as the last treatment option for LBP.

Many patients search for non-surgical conservative treatment at clinics where both modern procedures and integrative treatments are available.

In many Asian countries, the traditional system of medicine has developed in to a more integrative systems consist of herbal medicine\cite{14} spinal manipulation,\cite{15} bee venom acupuncture,\cite{16} and acupuncture.\cite{17}

We report this study, using up dated statistical modeling to evaluate the impact of acute LBP on HRQOL and determine the contributions of physical and psychosocial factors to the LBP recovery adjusted by some probable confounders, according to 24 weeks carefully followed, a preventive cohort of patients with LBP traditional treated.

**METHODS**

**Patients and interventions**

One hundred and fifty consecutive patients aged 18 years and older, self-referring to (i.e. first consultation with) for a primary complaint of LBP or had referred with lumbar disc herniation already confirmed by MRI, between November 2006 and October 2007 at Jaseng Hospital in Korea, which offers both, Western and Korean medical services. Of the 150 patients who were registered in the study, 116 had sub-acute or chronic LBP, and 34 experienced acute LBP. These recruited patients had not been previously treated for LBP at this hospital. Exclusion criteria were having LBP caused by non-spinal or soft tissue problems, VAS of pain 4 or less, pregnancy, spinal tumor, rheumatoid arthritis, unexplained weight loss; and major organ transplantation.

The therapeutic package consisted of weekly treatments and daily intake of herbal medicine for 24 weeks. Treatments included: 20 min sessions of acupuncture,\cite{18,19} 20 min sessions of a Korean version of spinal manipulation known as Chuna,\cite{20} bee venom acupuncture 20 min at physician's discretion,\cite{17} and special herbal medicines in dry powder form and water extracted form as prescribed by attending physicians from the 10 herbal medicines 2g and 120 ml, respectively, twice a day, 30 min after meal.\cite{21} We considered the following as independent variables: Visual analogue scale (VAS, 0-10) of back pain and leg pain, while the Oswestry Disability Index (ODI), sex, age and BMI. SF-36 Health Related Quality of Life Questionnaire was secondary outcomes was assessed as response variable. The time dependent variables were evaluated at baseline, 4th, 8th, 12th, 16th, 20th, and 24th week as longitudinal form.
Statistical molding description

A skew-symmetric random intercept mixed model was used to take into account the intra-patient and inter-patient variability in an outcome attributable to repeated measurements and to allow the inclusion of patients with missing values.

The skew-symmetric models as alternative to the normal model can be applied in application where the symmetry seems unreasonable.[26-30] Thus, the construction of asymmetric distributions can accommodate practical values of skewness and kurtosis can be useful for data modeling and robustness studies of normal theory methods.

For the purpose of inference, we used the Bayesian Markov chain Monte Carlo (MCMC) approach that provides a comparatively simple numerical tool that finds a solution as analytical difficulties inherent in the ML approach. To perform the skew-modeling, we mainly focus on some elliptical family, such as normal and Student’s t distributions, as well as the skew form of these densities as the skew-symmetric families of distributions for the random intercept. In the Bayesian framework, this is equivalent to the two-stage hierarchy form. These Bayesian hierarchical models, equivalent to the two-stage hierarchy form, for the data analysis based on MCMC techniques. The estimated random intercepts distribution according to the normal model by the estimated plots clearly showed deviation from normality in such a way that the distribution of intercept shows evidence of skewness. The goodness of fit between different models is evaluated by Bayesian model selection criteria. Model fitting was implemented by OpenBugs free software (www.ime.usp.br/mbranco).

The results of modeling determining the effect of traditional treatment on quality of life variable by considering VAS, ODI, age, sex, surgery recommended status, baseline HRQOL measures and BMI between different follow-ups. For each time-dependent variable, we analyzed the difference between the measurements obtained at the six time points.

RESULTS

The patients were 34.7 ± 8.4 years old (mean ± standard deviation). 58.4% of patients were male. The number of patients who had normal BMI category (18.5-23), overweight (>23), obesity and underweight (<18.5) was 63 (42%), 37 (24.7%) and 48 (32%), respectively. 61.3% from total subjects have recommended for surgery. Figure 1 show ODI and VAS levels (as two important factors which can show the effect of the traditional treatment), over time for 25 randomly selected subjects and suggests that ODI and VAS have uncertain trend over time for selected subjects.

Based on BUGS codes used for fitting different models, we use 10,000 iterations after discarding the first 5,000 iterations to make inference. To avoid correlation problems in the generated chains,

![Figure 1: Mean of response variables over time scale for the low back pain cohort study. Visual analogue scale of back pain (right), and oswestry disability index (left) ](https://www.mui.ac.ir)
the lag value was set to 5. Resulting parameter estimates (posterior means). According to the best model based on Bayesian model selection criteria (skew-normal random intercept model), VAS and ODI measures, age and BMI were significant based on the 95% Bayesian probability intervals in skew-symmetric modeling also, based on insignificant coefficients, there was no significant difference in HRQOL measures between different genders or different groups of surgery recommended. The sign of significant coefficients showed that decreasing the VAS associated with increasing HRQOL. Subjects with more BMI had better response to traditional treatment according to their HRQOL trend. Estimated coefficients for different covariates indicated that the variation of VAS was more effective than that of other considered factors (BMI and sex).

**DISCUSSION**

LBP and its related disabilities are major public health problems worldwide. The conventional treatment of LBP consists of medication, tissue stimulation (e.g., electrical stimulation, ultrasound), rest and orthotics. Failure of the non-surgical treatment leads to alternative options, such as a variety of surgical approaches to achieve spinal fusion with various results.

Given the inadequate results of traditional treatment and their side effects, there has been increasing usage of complementary and alternative medicine (CAM) by LBP sufferers to relieve their symptoms. There are more than 50 potential therapies promising to alleviate the pain, and provide a cure for this problem. So, several groups of health care providers, such as physicians, physiotherapists, chiropractors, and a host of more “alternative” caregivers are involved in management of LBP. Some experts take this over-abundance of therapeutic options as a sign that “nothing works very well” singly for LBP and recommend multi-disciplinary treatment programs.

The results of the current study showed that our integrative treatment package comprised of herbal medicines, acupuncture, bee venom acupuncture, and a Korean massage (Chuna) significantly decreased VAS and ODI and improved the HRQOL of patients.

Several traditional Chinese and Korean herbal medicine including *Cibotium barometz*, *Atractylodes japonica*, *Ostericumkoreanum*, *Eucommia ulmoides*, *Acanthopanax Sessiliflorus*, *Achyranthesbidentata*, *Psoraleacorylifolia*, *Peucedanum japonicum*, *Lycium chinense*, *Boschniakia rossica*, and *Cuscuta chinensis* have been used as treatments for LBP in this study. The above herbal medicines in powder and decoction forms are part of the historically developed treatment practiced at Jaseng Hospital for low back pain. It has been shown that the compounds of *Cibotium barometz* and *Atractylodes japonica* showed inhibition of osteoclast, and protection of the osteoblasts respectively. Furthermore, it has been reported that *Eucommia ulmoides*, *Dioscorea spongiosa* and *Cuscuta chinensis* have anti-osteoporotic effects through osteoblast-like cell proliferation, osteoclast inhibition effects and recover bone mineral density. *Psoralea corylifolia* and *Lycium chinense* have known anti-inflammatory effects while *Peucedanum japonicum* and *Boschniakia rossica* are good anti-oxidants.

Acupuncture is based on ancient Chinese philosophical theories about the flow of vital energy through the body along the discrete pathways termed meridians. In acupuncture, specific points alongside of the meridians are utilized to balance the energy flows within the body. Many different styles of acupuncture and adjunctive techniques have been developed and disseminated into other cultures.

There are several systematic reviews on efficacy of acupuncture in LBP patients comparing acupuncture with sham acupuncture, other sham treatments, no additional treatment, or another active treatment. Acupuncture effectively relieves chronic LBP. No evidence suggests that acupuncture is more effective than other active therapies.

Traditional Korean doctors have used apitoxin, or honey bee venom, as a type of pharmacopuncture. Bee venom is extracted from a honey bee by using electrical stimulation. It has been shown that Bee venom administration is effective in pain relief of rheumatoid and degenerative arthritis, which require long-term treatment, as well as resolution of inflammation.

Several mechanisms have been suggested to clarify the bee venom induced antinociceptive and
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anti-inflammatory effects, including the activation of spinal alpha 2-adrenoceptors of descending noradrenergic, adrenergic, and serotoninergic pathways and activation of capsaicin-sensitive primary afferent (CSPA) fibers.\(^{[47-49]}\)

The analgesic effects induced by BV acupuncture also may be attributable to bioactive BV compounds, including peptides (melittin, adolapin, apamin, and the mast-cell degranulating peptide), enzymes (phospholipase A2), and amines (histamine and epinephrine)\(^{[50]}\).

Massage is a simple way of pain relief, which stimulates large diameter nerve fibers that finally inhibits nociceptive fibers. It may also provide its benefits through shifting the autonomic nervous system from a state of sympathetic response to a state of para-sympathetic response, and increasing the pain threshold through the release of endorphins\(^{[34]}\).

The results of a systematic review showed that massage is beneficial for patients with sub-acute and chronic nonspecific LBP in terms of improving symptoms and function. Two studies compared massage to sham treatment reported that massage was superior for pain and function on both short and long-term follow-ups. However, a latest Cochrane review of spinal manipulation in chronic LBP concluded that spinal manipulative therapy results in a small, statistically significant but not clinically significant pain relieve and function in patients with chronic LBP compared with other treatments.\(^{[51]}\)

To the best of our knowledge, this is the first study investigating the effect of an integrative treatment package on LBP. Furthermore, while most of the studies considered short term beneficial effects of traditional and CAM approach to relieve pain, the long observational period of 6 months allowed us to predict progress of treatment outcomes. However, we were unable to compare the results of our study to others and could not find which treatment of the package is more effective than others.

One more interesting finding of the re-analysis of the results with new method is the similar results in patients with and without the herniated disc surgery. It seems that this package may lead to impressive outcomes even in patient with serious underlying patho-physiology similar other study.\(^{[58]}\)

CONCLUSION

Our results suggest that multi-modal treatments may improve LBP by several mechanisms. 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.

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