Single-Blind Randomized Controlled Trial of Poly-Herbal Formula Sahatsatara for Acute Low Back Pain: A Pilot Study

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ABSTRACT

Objective: To evaluate the efficacy and safety of poly-herbal formula Sahatsatara (SHT) in pain reduction in acute low back pain (LBP) patients.

Methods: Twenty-nine patients aged 18-65 years with a history of moderate to severe acute LBP ≤3-day (score ≥4 on a 0-10 numeric rating scale [NRS]) were enrolled and randomized to receive an ibuprofen (400 mg after meals three times daily) or SHT (1,350 mg before meals three times daily) for 7 days. The non-inferiority trial margin was set at ±10 percentage points. The outcomes were measured on pain intensity on the 0-10 NRS, disability on the Thai version of the Oswestry disability index [ODI], total analgesic consumption, patient satisfaction, and safety.

Results: Fourteen patients and 15 patients were randomly allocated to ibuprofen and SHT groups, respectively. The mean difference in pain intensity and disability between the two groups at day 7 adjusted according to baseline was within ±1 for pain (-0.3; 95% CI, -1.48 to 0.96) and ±10% (-4.9%; 95% CI, -14.86% to 5.02%) for the NRS and ODI scores, respectively. One patient in the SHT group and 5 in the ibuprofen group had gastrointestinal irritation, but the difference was not statistically significant.

Conclusion: SHT was not inferior to ibuprofen in pain relieving and disability in patients with acute LBP. The result suggests a role for SHT as an alternative analgesic in acute LBP.

(Thai Clinical Trials Registry number 20141027001)

Keywords: Acute low back pain, poly-herbal formula Sahatsatara, ibuprofen

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INTRODUCTION

Acute low back pain (LBP) is one of the common medical complaints which result in substantial pain, and social-economic burdens.[1] The majority of LBP patients have no identifiable specific pathophysiological cause and are thus classified as having non specific LBP.[2] Paracetamol is the first-line drug for treatment of nonspecific acute LBP. However, it has potentially hepatotoxic side effects and is reportedly less effective than nonsteroidal anti-inflammatory drugs (NSAIDs), a second-line treatment.[3] However, traditional NSAIDs have been well-documented for their gastrointestinal

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side effect (SE), and specific COX-2 inhibitors have been reported for cardiovascular adverse events (AEs).[4] The findings of systematic review have led to a reappraisal of the analgesic efficacy of NSAIDs compared with other pain relievers for acute LBP.[5]

Poly-herbal formula Sahatsatara (SHT), comprising of 19 herbal medicines, has been used as analgesic in Thailand for 3 decades and it is also official in the Thai National List Essential Medicines as analgesics. There is substantial clinical experience for its use for muscle pain in the Ayurved Clinic, Siriraj Hospital. However, there is little direct evidence from a few clinical trials to support its use as analgesic.

We hypothesized that SHT may be an effective treatment for nonspecific acute LBP and conducted a randomized, single-blind, non-inferiority pilot study to compare its benefits, and safety with those of ibuprofen.

MATERIALS AND METHODS

The study was performed at the Department of Rehabilitation Medicine, Siriraj Hospital, during 1 March to 20 December 2013. The study was approved by the Ethic Committee on Human Research of the Faculty of Medicine Siriraj Hospital, and written inform consents were obtained from all participants. The Thai Clinical Trials Registry identification number is TCTR2014102700 (http://www.clinicaltrials.in.th). A sample size of 30 participants was chosen for pilot study. Eligible patients were men and women aged 18–65 years who were diagnosed with nonspecific acute LBP and had a history of moderate to severe acute LBP ≤3-day at baseline (score ≥4 on an 11-point numerical rating scale [NRS] where 0 = no pain and 10 = worst pain imaginable). All of inclusion criteria were agreed with the rehabilitation medicine specialist. Patients were excluded if they had chronic LBP, had a history of spinal trauma or lumbosacral surgery within the previous year; a history of osteoporosis, asthma, immunodeficiency, diabetes mellitus, hypertension, cardiovascular disease; gastrointestinal disorder; a history of epilepsy; liver disease; renal disease; hypersensitivity to ibuprofen or SHT, or any of its constituents; pregnancy or lactating; or use of contraceptive.

SHT 450-mg tablets were produced by the pharmaceutical unit at the Center for Applied Thai Traditional Medicine, Faculty of Medicine Siriraj Hospital. Quality control is based on the pharmaceutical standards of the British Pharmacopoeia 2008 and using Good Manufacturing Practice, performance of thin-layer chromatographic fingerprint analysis and ultra-high-performance liquid chromatography. The tablets were stored at a room temperature (25°C) in a dry and clean place.

Participants were randomly allocated and treated with either a 1,350-mg oral dose of SHT before meals three times daily for 7 days, or a 400-mg oral dose of ibuprofen (Nurofen; Reckitt Benckiser Healthcare Manufacturing, Samutprakarn) after meals three times daily for 7 days, by block randomization. Paracetamol (Tylenol; Johnson & Johnson, Ayutthaya), 500-1,000 mg every 4 to 6 hours (maximum dosage of 4 g/day), was provided as a rescue medication if needed. All interventions were in sequentially numbered containers. Only the physician who diagnosed and assessed the treatment outcomes was blinded.

The outcomes were pain intensity as measured with an 11-point NRS and disability as measured with the ODI 1.0 Thai version,[6] which measures the disturbance of physical activities of daily life through the presence of pain disability.[7] Pain outcomes were evaluated before treatment (day 0) and on days 1, 3, and 7 after treatment. Total analgesic consumption, patient satisfaction with treatment (using an 11-point NRS where 0 = strongly unsatisfied and 10 = strongly satisfied), adverse events, and adherence were also recorded by interviewing and pill count. The follow-up date might be postponed by 1 day, if it was a holiday.

At enrollment (day 0), each participant's age, sex, and work experience were recorded, and pain intensity and disability were measured. Vital signs were recorded and blood samples were collected to evaluate safety. Patients were also advised to rest on the first day and were given information about back care and positioning at work. The same assessments were made at each visit apart from blood sampling, which was repeated

on day 7. Patient satisfaction was recorded on day 7. The participants were allowed to withdraw if harmful side effects occurred. The trial stopped when most of the participants experienced more harm than benefit associated with the treatment.

The mean differences in pain intensity and ODI scores on day 7 adjusted to the baseline value (day 0) were subject to covariate analysis (ANOVA). Non inferiority trials are intended to examine whether the effect of a new treatment is not worse than a standard treatment by more than a specific margin,[8] which were set at ±1 point, and ±10%, on the NRS, and on the ODI, respectively. Fisher's exact test was used to compare the baseline categorical data and reported adverse events. Between-group differences in continuous baseline characteristic data, total analgesic consumption, and patient satisfaction were assessed using the unpaired t-test. Within-group changes in vital signs or laboratory investigations were compared using the paired *t*-test. *P* value <0.05 was considered statistically significant at 95% confidence intervals (CI). This study was analyzed as per-protocol.

RESULTS

Thirty-four patients were screened, 29 were enrolled, 14 and 15 were allocated to the ibuprofen and SHT groups, respectively (Fig 1). Two patients in the SHT group withdrew from the study. The participants' baseline characteristics were not significantly different between groups (Table 1). After treatment for 7 days, the mean pain intensity score decreased from 5.5 to 1.6 in the SHT group and from 5.6 to 1.9 in the ibuprofen group. According to disability, the mean ODI score fell from 30.4% to 12.5% in the SHT group and from 30.1% to 17.4% in the ibuprofen group. The mean difference in pain intensity between the groups was within ±1 (-0.3; 95% CI, -1.48 to 0.96). The mean difference in disability between groups was within ±10% (-4.9%; 95% CI, -14.86% to 5.02%) (Table 2). Change of pain intensity and disability during treatment are shown in Figs 2 and 3, respectively. These findings suggest that SHT is not inferior to ibuprofen in terms of treating pain and disability.

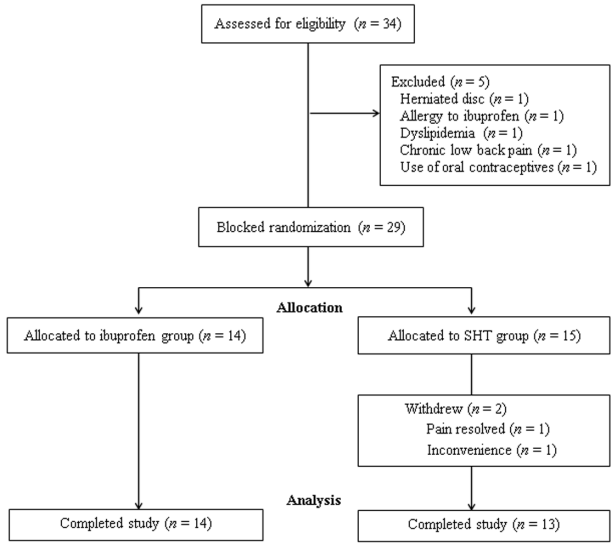

Fig 1. Flow of participants through the study.

In the SHT group, only one patient took a 500-mg rescue dose of paracetamol. In the ibuprofen group, one patient required rescue analgesia twice and another once, but this difference was not statistically significant (p = 0.445; 95% CI, -0.502 to 0.227; data not shown). The mean sat-

TABLE 1. Baseline characteristics of the 27 patients.

Characteristics	SHT (N=13)	Ibuprofen (N=14)	P value*
Sex: Male, *n* (%)	4 (30.8)	5 (35.7)	1.000[a]
Female, *n* (%)	9 (69.2)	9 (64.3)	
Mean age (SD), years	38.5 (8.9)	44.9 (9.2)	0.082[b]
Mean BMI (SD), kg/m^2	24.7 (4.5)	24.0 (3.4)	0.669[b]
Mean Pain intensity, 0–10 NRS (SD)	5.5 (0.9)	5.6 (1.2)	0.801[b]
Mean Disability, % score on ODI (SD)	30.4 (11.1)	30.1 (13.2)	0.940[b]

Abbreviations: SD = standard deviation; BMI = body mass index; NRS = numeric rating scale; ODI = Oswestry Disability Index 1.0 Thai version; [a]Fisher's exact test; [b]Unpaired t-test. *$p < 0.05$.

TABLE 2. Analysis of covariance of pain intensity and disability.

Outcomes	SHT (n = 13)	Ibuprofen (n = 14)	Mean difference[b] (95% CI)
Mean adjusted for baseline at after treatment (day 7)[a] and 95% CI			
NRS (0–10)	1.6 (0.73–2.45)	1.9 (1.02–2.71)	−0.3 (−1.48 to 0.96)[b]
ODI (0%–100%)	12.5 (5.34–19.66)	17.4 (10.52–24.31)	−4.9 (−14.86 to 5.02)[b]

Mean difference = difference in mean change from baseline to day 7 between SHT and ibuprofen groups in the covariance model analysis.

[a]Baseline values: mean NRS at day 0 = 5.6; mean ODI at day 0 = 30.3.

[b]Noninferiority margin was set at ±10% (1 point for 0–10 NRS; 10% for ODI)

Abbreviations: 95% CI = 95% confidence interval; NRS = 0–10 numeric rating scale; ODI = Oswestry Disability Index.

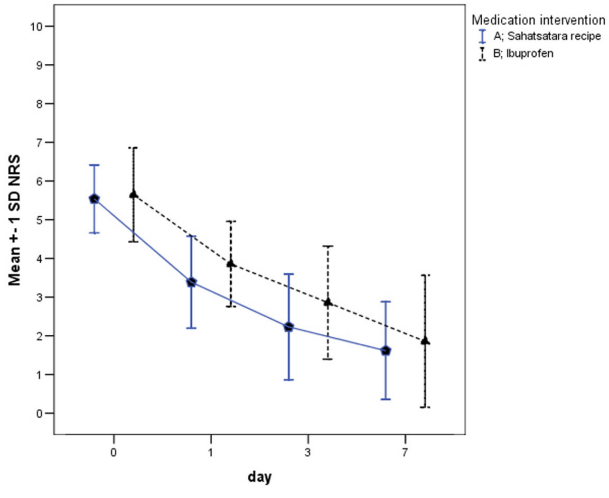

Fig 2. Mean pain intensity during 7 days of treatment for acute low back pain with SHT (A) or ibuprofen (B) (error bars show ±1 standard deviation).

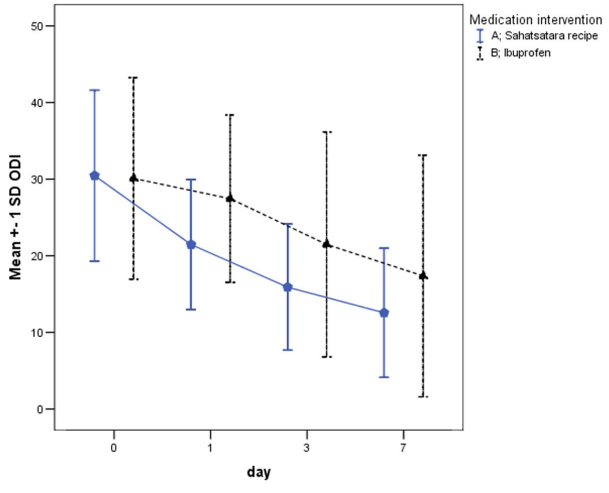

Fig 3. Mean Oswestry Disability Index score during 7 days of treatment for acute low back pain with SHT (A) or ibuprofen (B) (error bars show ±1 standard deviation).

isfaction score in the SHT and ibuprofen groups were 7.9 out of 10.0 (±1.4 S.D.) and 8.1 out of 10.0 (±1.9 S.D.), respectively. This difference was not statistically significant (p = 0.734; 95% CI, -1.553 to 1.114; data not shown).

There were no statistically significant differences in any of the vital signs between groups during the 7-day study period. The laboratory investigation tests showed some changes in both groups, but were still within a normal range and also no clinical importance (data not shown). Eleven patients in the SHT group reported about adverse events compared with seven in the ibuprofen group (Table 3). No serious adverse events were reported in either group. One patient taking ibuprofen reported about gastrointestinal symptoms, severe enough to warrant treatment with omeprazole. One in the SHT group reported a hot sensation in the stomach. There were no statistically significant differences in the incidence of gastrointestinal symptoms, other symptoms, or compliance between the groups.

DISCUSSION

There is well-known nonspecific acute LBP that is characterized as unknown cause of lumbar strain or sprain producing inflammation and pain.[9] This preliminary study was performed to compare the efficacy and safety of SHT with ibuprofen. As ibuprofen is considered to be a standard treatment that is safe and well tolerated, and

TABLE 3. Adverse events reported during treatment with SHT or ibuprofen.

Reported adverse events	SHT (n = 13)	Ibuprofen (n = 14)	*p* value*
Patients with any adverse events	11 (84.6)	7 (50)	0.103
Chest tightness	1 (7.7)	1 (7.1)	1.000
Constipation	1 (7.7)	0 (0.0)	0.481
Diarrhea	1 (7.7)	0 (0.0)	0.481
Nausea	1 (7.7)	1 (7.1)	1.000
Gastrointestinal symptoms	1 (7.7)	5 (35.7)	0.165
Thirst	0 (0.0)	2(14.3)	0.481
Dry mouth and throat	0 (0.0)	1 (7.1)	1.000
Headache	2 (15.4)	1 (7.1)	0.596
Tiredness	2 (15.4)	0 (0.0)	0.222
Hot flashes	2 (15.4)	0 (0.0)	0.222

Data are presented as *n* (%).

*Fisher's exact test; significant at *p* value of <0.05.

exhibits the lowest relative risk of gastrointestinal adverse reactions in epidemiologic studies.[10]

We found that the pain intensity in both groups decreased rapidly within the first 3 days of the trial, and then more gradually over the next 4 days (Fig 2). The mean difference in the pain intensity score between the groups on day 7 adjusted for baseline was -0.3 (95% CI, -1.48 to 0.96). The upper 95% CI limit was within the ±1 point of noninferiority trial margin for NRS, suggesting that the efficacy of SHT equals ibuprofen. The mean difference in disability between the groups on day 7 adjusted for baseline was -4.9% (95% CI, -14.86% to 5.02%). Again, the upper 95% CI limit for disability was within the predefined ±10% margin for noninferiority. Surprisingly, the analgesic effects of SHT appeared to plateau after 3 days of administration compared with ibuprofen (Fig 3). This finding may suggest that SHT has a faster onset than ibuprofen; even though the differences were not statistically significant.

Although there is little clinical evidence to support the use of SHT as a pain reliever, the components in the preparation have shown analgesic, anti-inflammatory, or antioxidant properties, which act synergistically. Piperine (present in the preparation as *P. nigrum* and *P. retrofractum*) reportedly desensitizes the TRPV1 vanilloid receptor, mostly expressed in the C- and Aδ-fibers of primary sensory neurons.[11] Furthermore, camphor and asafoetida (*F. assa-foetida* and *F. sinkiangensis*) are reported to strongly inhibit TRP ankyrin 1 (TRPA1) channels, which have a role in the peripheral pain sensation[12,13]. Components of SHT have also been shown to have anti-inflammatory activity, mediated by inhibition of COX-2 and release of tumor necrosis factor alpha (TNF-α), and nitric oxide (NO). Another possible target for SHT is NF-κB, a nuclear transcription factor that regulates genes involved in the inflammatory and nociceptive responses and the expression of which is reportedly attenuated by piperine (*P. nigrum* and *P. retrofractum*),[14] *A. calamus*,[15] *A. graveolens*,[16] *M. fragrans*,[17] *P. kurroa*,[18] P. *anisum*,[19] *P. indica*,[20] and *T. chebula*.[21]

Another possible action of SHT is an antioxidant due to phenolic compounds which have been recognized as free radical scavengers.[22,23] It is well established that muscle spasm generates free radicals of both reactive oxygen and nitrogen species provoking oxidative damage to active myofibers.[24] The synergistic effect of all 21 components of SHT (which mediate analgesia via TRP receptors; exhibit anti-inflammatory activity by mediation of COX, NO, NF-κB, and interleukins; and scavenge free radicals) which may help to explain its more rapid of onset than ibuprofen, which acts only on the COX pathway.

Moreover, we found patients who took SHT were able to mobilize and engage in daily

life activities. This reflects our finding that SHT afforded greater relief of disability than ibuprofen. However, taking three tablets of SHT, three times daily was the cause of a reduced mean satisfaction (8 out of 10). The need to take herbal medicines three times daily before meals is a well-recognized disadvantage, although it ensures good bioavailability. In contrast to the ibuprofen group, ibuprofen improved disability more slowly but also had a satisfaction rating of approximately 8 out of 10.

Concerning safety, one of the side effect of SHT is hypertension.[25] We found no significant difference in the blood pressures of the patients in each group, suggesting that SHT does not provoke hypertension in patients with an initially normal blood pressure. Again, although more adverse events were reported by those taking SHT compared with ibuprofen group, this difference was not statistically significant (p-value= 0.103) (Table 3). No serious adverse events were reported in either group. Despite the relatively lower incidence of gastrointestinal side effect associated with ibuprofen than other NSAIDs, five (35.7%) patients reported such symptoms: four were able to continue with the 7-day course of treatment, but one required treatment with omeprazole. Although this difference between groups was not statistically significant, it may be clinically important and warrants further study in a larger trial. However, it has also been reported that *A. graveolens*,[26] *A. lancea*,[27] *L. sativum*,[28] *N. sativa*,[29] and *P. anisum*,[30] exhibit gastrointestinal protective activity and increase gastrointestinal motility; these beneficial effects may result from taking SHT before meals. In contrast, NSAIDs have to be taken immediately after meals to avoid gastrointestinal side effects. The safety and tolerability of SHT appears to be better than those of ibuprofen.

Limitations of this study include its small sample size, lack of a placebo group due to an ethical issue, and impossibility of disguising the quite pungent odor of SHT. Nonetheless, it appears that SHT has analgesic properties and could be programed for a larger trial.

CONCLUSION

The dosage regimen of SHT (1,350 mg three times daily before meals for 7 days) was a safe and effective means of treating nonspecific acute LBP, with efficacy similar to that of ibuprofen. These results suggest a role for SHT as an alternative analgesic in acute LBP.

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