S-5 [14:00~14:30]

Effect of herbal medicine in Animal Models and Patients with Allergic Rhinitis

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Background and objective : Mahuangbujaseshintang(MBST) and soshihotang (SST) have been used for treatment of chronic disease of respiratery tract. It is necessary to clarify the mechanism of anti-allergic effects and to standardize the extracts.

Materials and Methods : The effects of MBST and SST were evaluated on histamine release in rat mast cell *ex vivo*. Several hours after administration of the extracts, mast cells were stimulated by DNP-ascaries and histamine contents were measured. Time course structural change of the cells was examined by dynamic study. In order to evaluate the effect of the extracts on the nasal patency, acoustic rhinometry was performed after administering of leukotriene D_4 to both nasal cavities of guinea pig(GP). We examined the effects of the extracts with double-blind study, and also studied change of nasal patency after challenge of antigen by acoustic rhinometry in patients with allergic rhinitis.

Results : MBST at 4hr and SST at 3hr after oral administration remarkably inhibited histamine release from rat mast cells in a dose-dependent manner. MBST treated GPs failed to show biphasic phenomena which indicated to reduce nasal volume as leukotriene antagonists. Both groups of patients who took MBST and SST for 1week or 2weeks showed significant decreased symptom severity index(SSI) from treatment week 2($p<0.05$). The percent volume change after challenge of the antigen was decreased in patients took the extracts for 2weeks. We obstained longer suppression of the symptom than antihistamine.

Conclusion : We conclude that the herb medicines of MBST and SST can be effective on allergic rhinitis.

Introduction

Mast cells are known to play an important role in the immediatetype allergic reaction, which is the major mechanism for causing allergic rhinitis and bronchial asthma. The bridge of surface IgE receptors by antigens elevates intracellular free Ca^{2+} concentration, leading to release of the chemical mediators, including histamine, leukotrienes and prostaglandins.[1,2] Histamine, peptid LTs, platelet activating factor were known to induce obstruction in allergic reaction in the nose in an allergic reaction. The leukotrienes (LTC_4 and LTD_4), enhanced permeability, and lead to fluid extravasation and tissue edema.[3] They were considered to involved the development of the late reaction.[4] The treatment of allergic rhinitis (AR) has been improved by our increasing understanding of the underlying pathophysiology of the allergic response. A number of the patients can be treated with a variety of drugs. Hence, there remains a need to develop new therapeutic agents for better prevention and treatment of allergic disorders. Some herbal medicine has been used in patients with chronic respiratory disease like AR and bronchial asthma. Recently an attempt has been made to prove the efficacy of herbal extracts for treating AR. In this study, we evaluated the effects of some herbal medicines mahuangbujaseshintang (MBST) and soshihotang (SST) on animal allergic model and patients with AR.

Materials and Methods

Animal models of immunized rats and guinea pigs were used. The study the effects of MBST and SST were studied on histamine release in mast cell ex vivo as well as on the time course stuctural changes. Finally, the patients were evaluated the efficacy by relief of symptom severity index(SSI)[5] and percent change of symptom and nasal patency.

The effects of these medicines were evaluated by histamine release in mast cells *ex vivo*. A single dose of MBST and SST dissolved in 2ml of distilled water was administered orally to each group of Wistar rats. Groups of two rats each were administered SST, doses of 0.5, 1.0, 5.0 or 10g/kg. Other groups of 2 rats each were administered MBST, dose of 12, 24, 120 or 240mg/kg. Control rats were only administered 2ml distilled water. Several hours after administration of SST or MBST in distilled water, rats were killed. Tyrode's solution was injected into the peritoneal cavity. Peritoneal cells, including mast cells, were then collected by aspiration. These cells

were layered on metrizamide solution and the mast cells were harvested. The suspension of mast cells was incubated and DNP-ascaris was added to this suspension. And then the histamine contents of the supernatant and pellet were measured.

We studied structural change of mast cells of immunized Wistar rat. Rat were immunized with DNP-ascaris and given MBST orally. IgE antibody against DNP-As was prepared as method describe by Tada.[6] Gradient method with metrizamide solution. The suspension of the mast cells prepared with Tyrode's solution was incubated followed by the addition of DNP-ascaris. Microscopical structural changes were examined by dynamic study with 30 sec to 30 min interval.

The purpose of another investigation was to adapt a method based on acoustic reflection to the study of Hartly guinea pig nose and to measure change in the size of nasal airway volume after instillation of LTD_4 in GP by acoustic rhinometry.[7] They were non-sensitized(n=24) or sensitized(n=20)[8] and this procedure was performed after oral administration of MBST or SST. GPs sensitized with oval albumin were divided into two groups. GPs of each group were administered MBST and saline for 2 weeks. Thereafter they were subdivided into 2 groups : LTD_4 instilled group and saline instilled group. LTD_4 or saline was instilled in both nasal cavities and acoustic rhinometry measurement was performed three times on each side at 30 min. before and 3hr and 6hr after instillation of LTD_4 or saline. The nasal cavity volume between the nostril and 2㎝ into the nasal cavity was calculated by computer for each measurement. Nasal patency of each animal was evaluated with the sum of the volume of the right and left nasal cavities. Changes in volume after the instillation were expressed as the percentchange from the values before the instillation.

72 eligible, 49 men and 23 women patients were enrolled 18 to 65 years of age. Each patient signed an informed consent before any procedures were performed. Diagnostic criteria used to select patients with AR were as follows: a minimum 2-year history of AR, a positive reaction to allergy work-up (skin test, RAST or MAST, nasal provocation test), and rhinitis symptoms (nasal congestion, rhinorrhea, and sneezing) of at least moderate severity as evaluated by the patient. Patients were excluded from the study if they presented with nasal polyps, obstructive nasal defect, acute or chronic sinusitis, a respiratory or systemic infection with 4wks immediately preceding screening, or past adverse reaction to nasal or systemic glucocorticoids.

The patient were divided into 2 groups; MBST group(n=24) and SST group(n=20). MBST group recieved MBST orally for 1wk or 2wks and SST group recieved SST for same duration as that of MBST. We studied the effects of MBST and SST with double-blind, randomized, placebo-controlled group study, and also studied change of nasal patency after challenge of antigen. The efficacy measures included relief of combined nasal symptoms (symptom severity index, SSI) and percent improvement from last dose of baseline to day 14 and endpoint (day 28). The patients were asked to keep a diary of ir symptom severity (nasal obstruction, rhinorrhea, and sneezing). The nasal cavity volume was measured by acoustic rhinometry. The nasal patency of each subject was evaluated with the sum of the volume of the right and the left nasal cavities. Changes in volume after antigen challenge were expressed as the percent change from the values before the challenge. Acoustic rhinometry was performed before administration of medicine, on day 14 and 28.

Results

MBST at 4h and SST at 3h after oral administration inhibited histamine release from rat mast cell significantly. The inhibitory effect was seen dose-dependently (Fig. 1,2). Both medicines of MBST and SST blocked the effect on antigen induced Ca2+ response of the mast cells. On dynamic study of structural change the surface of the mast cells was covered by a coating of MBST. And it was impossible that the granules were expelled out from the cells when they were stimulated with DNP-ascaris. In the sensitized GP, the value of nasal patency abruptly decreased at 30 min after the instillation and recovered to the value at 3hr after the instillation in non-treated GPs. The nasal patency then decreased again significantly at 6hr after the instillation. On the other hand, MBST treated GPs failed to change the value on 6hr after the instillation in MBST treated GPs(Fig. 3). Among the non-sensitized group, non-treated GPs showed similar findings of biphasic phenomenon and MBST treated GPs failed to change their patencies upto 6hr after the instillation of LTD4.

In study with patients SSI was significantly decreased from treatment 2weeks in MBST group(Fig. 4). In SST group, patients who took the medicine for 2wks showed significant decrease SSI from treatment 2wks and patients who took for 1wk showed

significant decrease on treatment wk 4(Fig. 4,5). Both of MBST and SST group showed significant increase the percent improvement from last dose of base line to week 2 and week 4. Two week administration of MBST and SST showed better effect than 1week administration. The percent volume change after antigen challenge was remarkably decreased in patients who took MBST and SST for 2wks(Table 1,2).

Conclusion

In this study, we evaluated efficacy of two herbal medicines, MBST and SST in animal models of AR and patients with AR. Our data from these findings suggest that these medicines may have some inhibitory effects in animal models of AR as a mast cell stabilizer in rat and a leukotriene antagonist in GP. We also performed double-blind study with MBST and SST in some AR patients. Our data demonstrate that both MBST and SST may have favorable effects in patient with AR for upto 1 month after taking the last dose. And two-week' administration may be more effective than one-week' administration in controlling symptoms of AR. Further investigation on a large scale for a long period will be needed to evaluate therapeutic roles.

table 1. Percent volume changes in MBST treated patients

	Number	Percent volume changes (%)	
		Treatment 2wk	Treatment 4wk
Placebo (1 wk)	12	53.8±10.5	56.9±11.7
Placebo (2 wk)	12	49.3± 9.7	51.3±10.8
MBST (1 wk)	9	32.3±10.8	30.2±10.9
MBST (2 wk)	10	28.3±11.7 *	15.3± 7.5 *

There was no difference of nasal volume between before and after the challenge of the antigen in MBST 2 weeks treated patients. And the percent volume changes was significantly lower than placebo in these groups (*p≤ 0.05).

table 2. Percent volume changes in SST treated patients

	Number	Percent volume changes (%)	
		Treatment 2wk	Treatment 4wk
placebo (1 wk)	12	53.8±10.5	56.9±11.7
placebo (2 wk)	12	49.3± 9.7	51.3±10.8
SST (1 wk)	9	28.3±11.8	27.5±11.3
SST (2 wk)	8	21.3±10.9 *	17.3± 7.2 *

There was no difference of nasal volume between before and after the challenge of the antigen in SST 2 weeks treated patients. And the percent volume changes was significantly lower than placebo in these group (*p≤ 0.05).

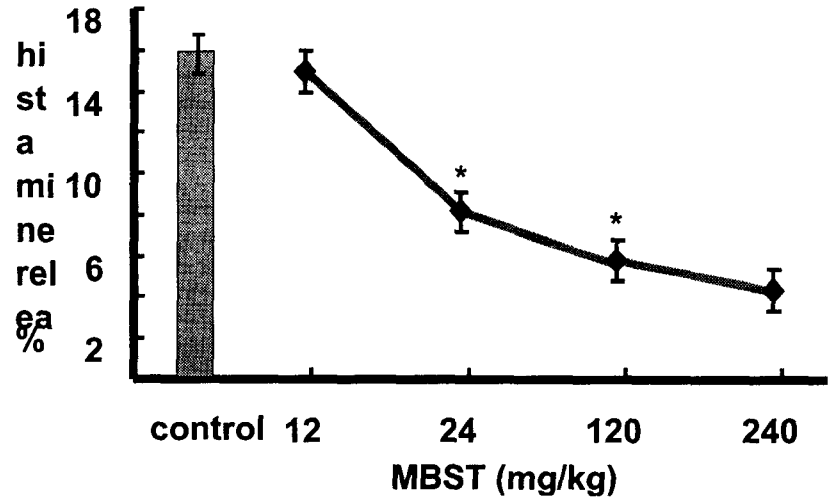

Fig 1. Effect of MBST on histamine release from ex vivo rat mast cells. MBST in strengths of 12, 24, 120, 240 mg/kg were administered as single dose to immunized rats 4h before sacrifice. Histamine release was inhibited dose-dependently by MBST (*p≤ 0.05).

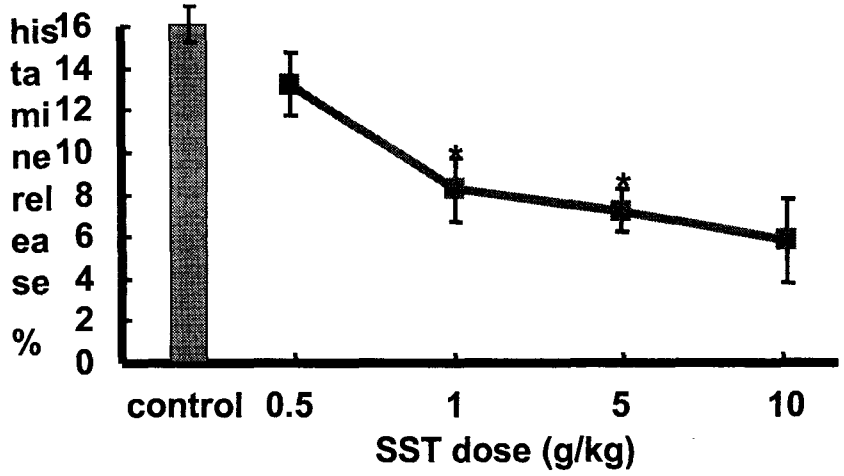

Fig 2. Effect of SST on histamine release from ex vivo rat mast cells. SST in strengths of 0.5, 1.0, 5.0, 10.0 g/kg were administered as single dose to immunized rats 3h before sacrifice. Histamine release was inhibited dose-dependently by SST (*p≤ 0.05).

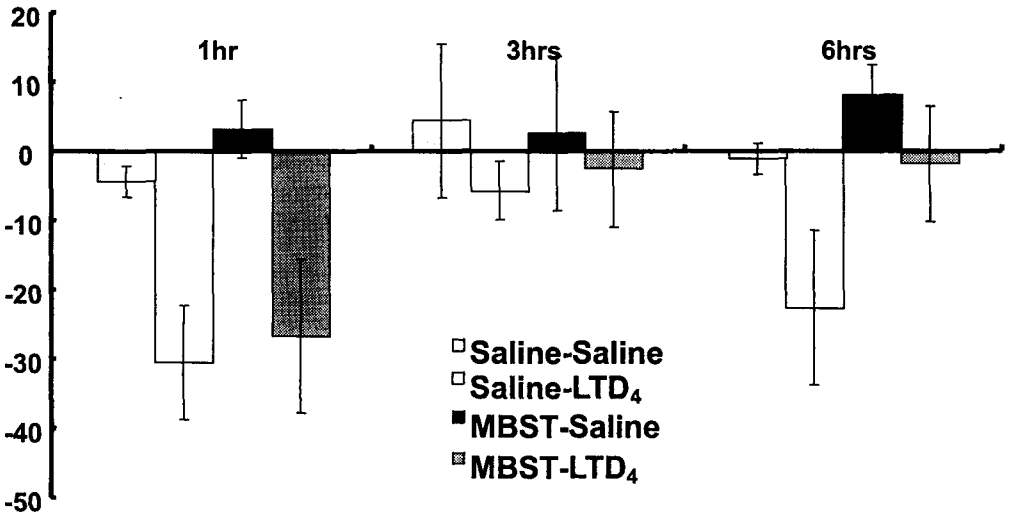

Fig 3. Percent volume changes of the nasal cavity after instillation of LTD_4 or Saline in immunized GPs. Late reaction was blocked in MBST-LTD_4 treated GPs

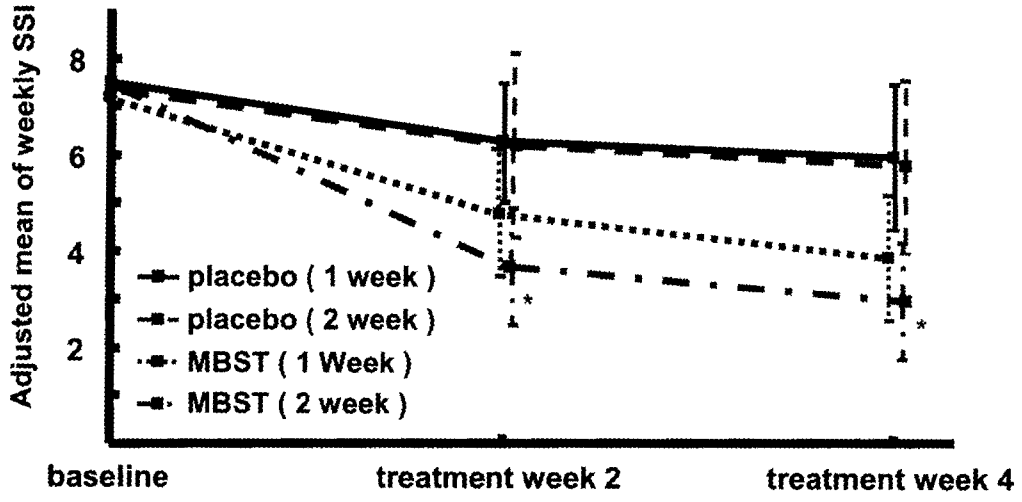

Fig 4. Relief of combined nasal symptoms (SSI) by study week in MBST treated patients. SSI was significantly decreased from treatment week 2 (*p≤ 0.05). However, there was no significant difference of SSI between 2 weeks and 1 week treated group.

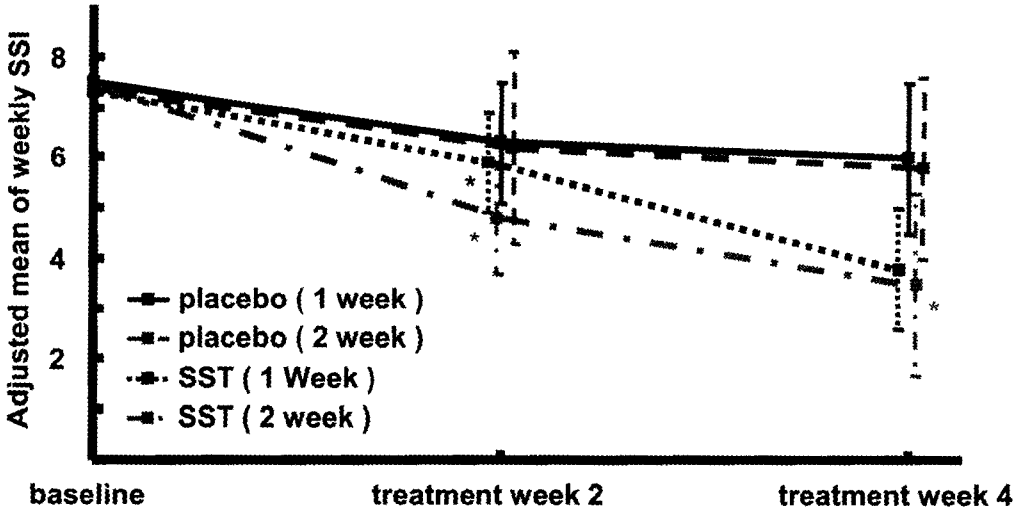

Fig 5. Relief of combined nasal symptoms (SSI) by study week in SST treated patients. SSI was significantly decreased from treatment week 2 (*p≤ 0.05). However, there was significant difference of SSI between 2 weeks and 1 week treated group (*p≤ 0.05).

References

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