

Effect of Mahuangbujaseshintang and Soshihotang in animal model of allergic rhinitis

Nam-Pyo Hong, Joong-Saeng Cho, Young-Wan Jin and Seung Ug Hong*

Dept. of Otolaryngology, College of Medicine,

*Dept. of Ophthalmology, Otorhinolaryngology and Dermatology, College of Oriental Medicine,**

Kyung Hee University, Seoul, Korea

Background and objective : Mahuangbujaseshintang(MBST) and soshihotang (SST) have been used for treatment of chronic disease of respiratory 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 cells *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 D₄ 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 4 hr and SST at 3 hr after oral administration remarkably inhibited histamine release from rat mast cells in a dose-dependent manner. MBST-treated GPs failed to show bi-phasic phenomena which indicated to reduce nasal volume at the time of early and late phases in allergic inflammation. Both groups of patients who took MBST and SST for 1 week or 2 weeks 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 31 patients who took the extracts for 2 weeks.

Conclusion : We can conclude that the herb medicine of MBST and SST may be effective for allergic rhinitis. (J Asthma Allergy Clin Immunol 20: 619-626, 2000)

Introduction

Allergic rhinitis(AR) has been referred to as "the most common IgE-mediated allergic disease" with prevalence estimates in the temperate country ranging up to 20%. It has been ranked as the fifth most prevalent

chronic disease in these areas¹⁾. Mast cells are known to play an important role in the immediate type allergic reaction, which is the major mechanism for causing allergic rhinitis and bronchial asthma. The bridge of surface IgE receptors by antigens elevates

통신저자 : 경희의료원 이비인후과 조중생

서울시 동대문구 회기동 (우 130-702)

e-mail : khuent@unitel.co.kr

접수 : 2000년 6월 5일, 통과 : 2000년 7월 13일

intracellular free Ca^{2+} concentration, leading to release of the chemical mediators, including histamine, leukotrienes and prostaglandins^{2,3)}. One of the characteristic features of AR is the extreme reactivity of the nasal mucosa to specific antigen and non-specific stimuli^{4,5)}. Patients with AR develop a greater swelling of nasal mucosa in response to a wide variety of stimuli than healthy subjects. Histamine, peptide LTs, and platelet activating factor are known to induce obstruction in the nose in an allergic reaction. The leukotrienes (LTC_4 and LTD_4) enhanced permeability, and lead to fluid extravasation and tissue edema⁶⁾. They were considered to be involved the development of the late reaction⁷⁾. 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 medicines have been used in patients with chronic respiratory disease like AR and bronchial asthma. Recently, an attempt was 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 some patients with AR.

Materials and methods

Animal models of immunized rats and guinea pigs were used. We study the effects

of MBST and SST on histamine release in mast cell *ex vivo* as well as on the time course structural changes. Finally, the patients were evaluated for efficacy by relief of symptom severity index (SSI)⁸⁾ and percent change of symptom and nasal patency.

1. The *ex vivo* effect of the MBST and SST on histamine release from rat mast cells

The effects of these medicines were evaluated by histamine release and by intracellular Ca^{2+} response in mast cells *ex vivo*. A single dose of MBST and SST dissolved in 2 ml of distilled water was administered orally to each group of Wistar rats. Groups of two rats each were administered SST in doses of 0.5, 1.0, 5.0 or 10 g/kg. Other groups of two rats each were administered MBST in doses of 12, 24, 120 or 240 mg/kg. Control rats were only administered 2 ml of 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. Mast cells treated with or without MBST or SST were incubated with Ca^{2+} indicator dye. Fluorescence intensities excited at 340 and 380 nm were measured with spectrofluorometer. (Hitachi 65-60, Tokyo, Japan)

2. Dynamic study of structural changes in rat mast cells after treatment of MBST

We studied the structural changes in mast cells of immunized Wistar rats. Rats were immunized with DNP-ascaris and given MBST orally. IgE antibody against DNP-As was prepared as in method described by Tada¹⁰⁾. Rats' feet were injected equally with 1.8 mg of ascaris serum extract and 10¹⁰ killed *Bordetella pertussis* as an adjuvant. Five days later, a booster of 0.9 mg of DNP-As was injected to the back muscle. After 5 additional days, a blood sample was collected from the tail vein to measure IgE sera antibody titers using a 48-h passive cutaneous anaphylactic (PCA) reaction¹¹⁾. Only rats with a reciprocal PCA titer of 200 were selected for further study. The mast cells were collected from the pleural and the peritoneal cells by 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.

3. The effect of MBST on the patency of the nasal passage in the Guinea pig

The purpose of this investigation was to adapt a method based on acoustic reflection of the study of Hartly guinea pig nose and to measure changes in the size of nasal airway volume after instillation of LTD₄ in GP by acoustic rhinometry¹²⁾. They were non-sensitized (n=24) or sensitized (n=20)¹³⁾

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 orally administered MBST and saline for 2 weeks. Thereafter, they were sub-divided into two groups : LTD₄ instilled group and saline instilled group. LTD₄ or saline was instilled in both nasal cavities and acoustic rhinometry measurement was performed three times on each side at 30 min before, 3 hr and 6 hr after instillation of LTD₄ or saline. The nasal cavity volume between the nostril and 2 cm 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.

4. Evaluation of the effects of herbal medicines on patients with allergic rhinitis

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 prick 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, respiratory or systemic infection for 4 weeks immediately preceding screening, or past adverse reaction to nasal or systemic glucocorticoids.

The patients were divided into two groups : MBST-treated group(n=24) and SST-treated group(n=20). MBST group received MBST orally for 1week or 2weeks. SST group received SST for the 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 changes 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 end point (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 4 hr and SST at 3 hr after oral administration inhibited histamine release from rat mast cell significantly. The inhibitory effect was seen dose dependently (Fig. 1, 2). Both MBST and SST blocked the effect on antigen induced Ca^{2+} 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 3 hr after the instillation in non-treated GPs. The nasal patency then decreased again significantly at 6 hr after the instillation. On the other hand, MBST treated GPs failed

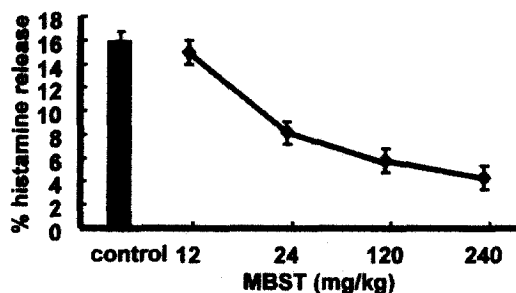


Fig. 1. Effect of MBST on histamine release from ex vivo rat mast cells. MBST in strengths of 12, 24, 120, 240 mg/kg were administered as single dose to immunized rats 4h before sacrifice. Histamine release was inhibited dose-dependantly by MBST.

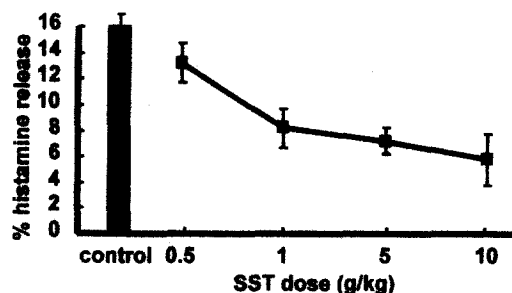


Fig. 2. Effect of SST on histamine release from ex vivo rat mast cells. SST in strengths of 0.5, 1.0, 5.0, 10.0 g/kg were administered as single dose to immunized rats 3h before sacrifice. Histamine release was inhibited dose-dependantly by SST.

to change the value at 6 hr 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 for upto 6 hr after the instillation of LTD₄.

In the study with patients, SSI was significantly decreased after 2 weeks of treatment in MBST group ($p < 0.05$, Fig. 4). In SST group, patients who took the medicine for 2 weeks showed significant decrease in SSI after 2 weeks of treatment and patients with 1 week of treatment showed significant decrease at treatment

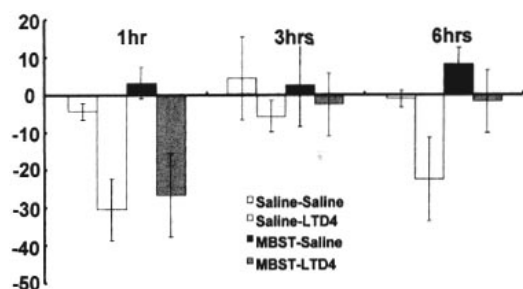


Fig 3. Percent volume changes of the nasal cavity after instillation of LTD₄ or Saline in immunized GPs. Late reaction was blocked in MBST-LTD₄ treated GPs.

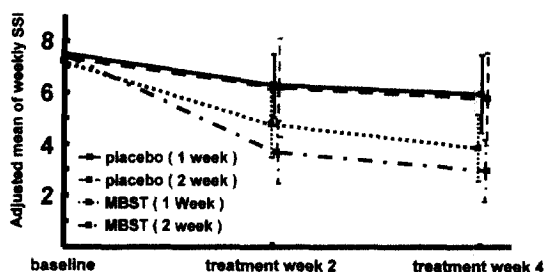


Fig. 4. Relief of combined nasal symptoms (SSI) by study week in MBST treated patients ($p < 0.05$). SSI was significantly decreased from treatment WK2. However, there was no significant difference of SSI between 2-week and 1-week treated group.

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

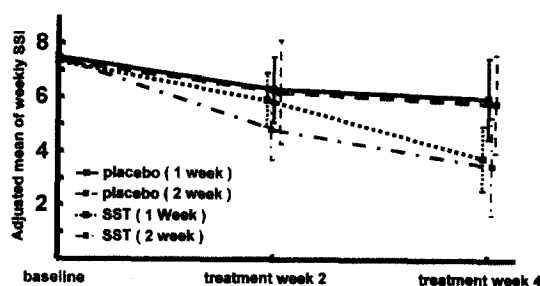


Fig. 5. Relief of combined nasal symptoms (SSI) by study week in SST treated patients ($p < 0.05$). SSI was significantly decreased from treatment WK2. However, there was significant difference of SSI between 2-week and 1-week treated group.

Discussion

Prior to the discovery and availability of H₁-blocking agents, the only way of reducing symptoms caused by aeroallergens was to avoid these allergens; however, this approach had sharp limitations in the case of pollen, mold spores, and house-dust allergens. The great clinical allergists early in the twentieth century identified important aeroallergens, prepared allergen extracts, and devised safe and effective treatment regimens involving their use¹²⁾.

Anti-histamines are currently the most frequently used medication for the treatment of AR¹³⁾. Although second-generation, rela-

tively nonsedating anti-histamines have surpassed sales of the relatively sedating, first-generation anti-histamines in the treatment of AR, many first-generation anti-histamines are available and continue to be used frequently as self medication. And the nasal glucocorticoids, generally considered the most effective pharmacologic treatment for AR, have been available for more than 30 years¹⁴⁾.

There have been several kinds of new trials for treatment of AR: leukotriene antagonist, anti-IgE antibody, anti-ICAM antibody, Th1 cytokine transfer, and DNA base immunization. Recently herbal medicine

or alternative medicine) has been considered as a method of treatment. The efficacy of herbal medicines in the treatment of AR has not been extensively studied.

Despite the lack of scientific validation for herbal product efficacy, people are using herbal-based interventions. The alkaloid occurs naturally in the ephedra plant and it has been in use in Chinese medicine for over 5000 years as a tea infusion (*Ma Huang*)¹⁵⁾. A number of studies support the use of some herbal medication in allergy¹⁶⁾. Improved symptoms were seen in allergic rhinitis specifically on histamine-induced reactions, such as rhinorrhea, sneezing and itching.

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 in nasal volume before and after the challenge of the antigen in patients with 2-week MBST treatment. And the percent volume changes were significantly lower than for the placebo group ($p \leq 0.05$)

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 in nasal volume before and after the challenge of the antigen in patients with 2-week SST treatment. And the percent volume changes were significantly lower than for the placebo group ($p \leq 0.05$)

Ma huang, minor blue dragon and gingo biloba has been used for asthma, allergy and cough. Aloe extract has been used for the treatment of asthma, cold and cough. Shida and Yagi¹⁷⁾ studied the effect of Aloe on phagocytosis in asthma. Bioflavonoid rich herbs, including chamomile and yarrow were known to be active anti-inflammatory and anti-allergic agents that could prevent the formation of allergy¹⁸⁾.

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 a double-blind study with MBST and SST in some AR patients. Our data demonstrate that both MBST and SST may have favorable effects in patients 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 longer period will be needed to evaluate therapeutic roles.

References

- 1) Evans R : Epidemiology and natural history of asthma, allergic rhinitis, and atopic dermatitis In: Middleton E, Reed CE, Adkinson NF, Yunginger JW, Busse WW (Eds.) Allergy Principles and Practice, 4th ed, p1109-36, St Louis : Mosby, 1993
- 2) Ishizaka T : Analysis of triggering events in mast cells for immunoglobulin E-mediated histamine release. J Allergy Clin Immunol 67: 90-6, 1981
- 3) Ranadive NS, Dhanari N : Movement of calcium ions and release of histamine from rat mast cells. Int Arch Allergy Appl Immunol 61: 9-18, 1980
- 4) Druce HW, Wright RH, Kossoff D et al : Cholinergic nasal hyperreactivity in atopic subjects. J Allergy Clin Immunol 76: 445-52, 1985
- 5) Ukai K, Sakakura Y, Miyoshi Y, Uchida Y : Pathophysiological condition of the nose of asthmatic children with sub-clinical nasal allergy. Rhinology 22 : 133-40, 1986
- 6) Bisgaard H, Olsson P, Bende M : Leukotriene D₄ increases nasal blood flow in humans. Prostaglandins 27: 599-604, 1994
- 7) Price JF, Hey EN, Soothill JF : Antigen provocation to the skin, nose and lung in children with asthma: immediate and dual hypersensitivity reactions. Clin Exp Immunol 47: 587-94, 1982
- 8) Tri-Nasal triamcinolone acetate nasal spray 200 and 400ug gd versus placebo and Nasacort triamcinolone acetate nasal aerosol 440ug gd in patients suffering from seasonal allergic rhinitis during the grass season. Ronsenthal R, Werger MD, Bronsky E. Am J of Rhinol 12: 427-33
- 9) Tada T, Okumura K : Regulation of homocytotropic antibody formation in the rat. I. Feed-back regulation by passively administered antibody. J Immunol 106: 1002-11, 1971
- 10) Cho JS, Cha CI, Lee DY : The effect of leukotriene D₄ in the patency of nasal passage in the guinea pig. Am J Rhinol 12: 421-5, 1998
- 11) Ishida M, Amesara R, Ukai K, Sakakura Y : Antigen (DNP-As)-induced allergic

- rhinitis model in guinea pigs. Ann Allergy 72: 240-4, 1994
- 12) Adams PF, Marano MA : Current estimates from the National Health Interview Survey. 1994 National Center for Health Statistics, Vital Health Statistics 10: 81-2, 1995
 - 13) Simons FER : H₁-receptor antagonists: Clinical pharmacology and therapeutics. J Allergy Clin Immunol 84: 845-61, 1989
 - 14) Naclerio RM : Allergic rhinitis. N Engl J Med 325: 860-9, 1991
 - 15) Eccles R : Nasal airflow and Decongestants. In Naclerio R., Duham S., Mygind N (Eds) Rhinitis. p291-312, Marcel Dekker Inc 1999
 - 16) Lane DJ : What can alternative medicine offer for the treatment of asthma. J Asthma 31: 153-60, 1994
 - 17) Shida T, Yagi A, Nishimura H et al : Effects of aloe extract on phagocytosis by peripheral neutrophils in adult bronchial asthma. Planta Med 3: 275-85, 1985
 - 18) Boardhurst CL : Natural allergy and asthma relief: How to safely control chronic respiratory conditions. Lecture at natural products p3, Expo, Anaheim, CA, March 5-8, 1997