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PEDIATRIC ALLERGY AND IMMUNOLOGY

Efficacy and safety of modified Mai-Men-Dong-Tang for treatment of allergic asthma

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The aim of this study was to evaluate the efficacy and safety of a Chinese herbal formula modified Mai-Men-Dong-Tang (mMMDT) for treatment of persistent, mild-to-moderate asthma. A total of 100 asthmatic patients were enrolled and assigned to three treatment groups in this double-blind, randomized, placebo-controlled clinical trial. Over a period of 4 months, patients in groups A and B received 80 and 40 mg/kg/day of mMMDT, while those in group C received a placebo. Efficacy variables included changes in forced expiratory volume in 1 s (FEV_1), symptom score, serum total immunoglobulin E (IgE), and dust mite-specific IgE. Safety assessments included complete blood count, and liver and kidney function. Relative to baseline, significantly greater increases in FEV_1 were demonstrated for both A and B groups in comparison with the placebo-treated analog (both $p < 0.05$). Further, similar improvements in symptom score were observed for both mMMDT treatment groups. The serum total IgE for group A showed a decreasing tendency after treatment but no statistical difference was noted. Furthermore, no drug-related adverse effects were reported. Blood test, and liver and kidney function were within normal range during the study, with no marked changes demonstrated over time. In conclusion, the Chinese herbal formula mMMDT provided improvements in lung function and relieved asthma symptoms in our sample of patients. Given its efficacy and safety, we consider mMMDT a credible treatment regimen for persistent, mild-to-moderate asthma.

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Allergen-induced, immunological disorders such as asthma, have long been considered as one of the most serious health problems in the world. In recent years, statistics show earlier onset of allergic asthma. In Taiwan, the prevalence of childhood asthma has increased from 1.3% in 1974, to 5.07% in 1985 and 5.8% in 1991 (1, 2). Because of the pandemic proportions for both the prevalence and morbidity of allergic asthma, usage of traditional Chinese herbal medicine (TCM) has become quite common because it is often perceived as natural and, therefore, considered safe.

TCMs improve immune system function and are used to treat various chronic immunological disorders (3). The scientific literature supporting the efficacy of herbal therapies is incomplete. Further, there are few well-controlled studies supporting the efficacy of herbal remedies for treatment of, and clinical improvement in, patients with asthma. One of the most comprehensive anti-asthma clinical trials, a multi-center, double-blind and placebo-controlled study, was reported in Taiwan (4). The results showed that the TCM treatments were beneficial in the improvement of symptom scores. However, statistically significant differences were not demonstrated between treatment and placebo for many other clinical indicators. To further improve the efficacy of TCM treatment for allergic asthma, we

studied the working mechanisms of several TCM formulas used for the treatment of bronchial asthma. From animal experiments, we found that modified Mai-Men-Dong-Tang (mMMDT) can significantly decrease the concentration of interleukin-4 in bronchoalveolar fluid after inhalational allergen challenge. In addition, mMMDT also significantly decreased airway inflammation compared with placebo groups (5). Therefore, a clinical trial was conducted to prove the safety and efficacy of mMMDT.

Materials and methods

Study design

This study was a randomized, placebo-controlled, double-blind study of children aged 5–18 yr who had experienced episodes of dyspnea, coughing, and wheezing, requiring intermittent or frequent bronchodilator treatment, and considered candidates for continuous treatment for control of these symptoms. Inclusion criteria (as assessed in the month before randomization) were: forced expiratory volume in 1 s (FEV_1) > 60% of the predicted value and reversibility ≥15% of baseline following inhalation of a bronchodilator; two or more positive skin tests; total serum IgE titer > 95th percentile for age; and, family and personal histories of atopy. All patients were instructed in asthma management, evaluated for compliance, and given radioallergosorbent and skin prick tests. Exclusion criteria were: acute respiratory infection within 3 wk of study onset; systemic glucocorticoid treatment in the 3 months prior to the study, or for more than 30 days in the preceding 2 yr; serious adverse reactions to theophylline or glucocorticoids in the past; diagnosis of attention deficit disorder, behavioral disorder, mental retardation, alcohol or drug abuse, or other psychological or emotional disorders requiring treatment. Female candidates were also excluded if they were pregnant, lactating, or sexually active and not using reliable birth control. The study protocol was approved by the Institutional Review Board. Before enrollment, oral consent was obtained from all children, and written informed consent from their parents.

Randomization

Randomization was performed by selection of a sealed envelope from a closed bag. Forty sealed envelopes were prepared for each of the two mMMDT groups, and 20 for the placebo group. Patients were aware that there was a greater chance of receiving active treatment.

Baseline measurements

For baseline measurement, lung function was assessed and reversibility of abnormalities in FEV_1 established (if not previously determined). Patients were randomly assigned to groups receiving mMMDT 80 mg/kg/day, 40 mg/kg/day or placebo, in twice-daily doses. The appearance of the placebo was almost identical to that of mMMDT. Blood was taken for measurement of total and allergen-specific IgE.

Study visits

Lung function was assessed and recorded for each visit during treatment and at follow-up. Lung function was measured at least 6 h after the β-agonist was last given. Spirometry was performed using standardized equipment and procedures recommended by the American Thoracic Society. Predicted normal values for age and measured height were used for assessment of FEV_1.

Management of asthma

During each visit, daily diary records of symptom scores and medication use were reviewed by a team of investigators unaware of treatment assignment. Asthma medications were provided gratis and adjusted in a stepwise fashion equally in all three groups as follows: step 1, use of bronchodilator as needed; step 2, regular use of brochodilator (theophylline or albuterol); step 3, regular use of two or three drugs (theophylline, albuterol and cromolyn); step 4, addition of beclomethasone delivered with a metered-dose inhaler or alternate-day methylprednisolone; and, step 5, addition of oral corticosteroids (> 0.5 mg/kg/day, with tapering). Acute exacerbation of asthma was treated as directed by the child's physician using tapered doses of oral methylprednisolone. Emergency room care and inpatient treatment were provided at the physician's discretion.

Herbal preparation and dispensing

All herbs were sourced as a dried powder and encapsulated. The standard herbal formulation (mMMDT) was designed by a doctor of Chinese medicine, and prepared by Sun-Ten Pharmaceutical Inc.(Taipei, Taiwan) (Table 1). The total amount of medicine required for the entire study was prepared at one time, aliquoted and packaged. The quality of each component herb was checked using high-pressure liquid chromatography to ensure compliance with government

Table 1. Components of herbal medicines in modified Mai-Men-Dong-Tang

Herb	Pharmaceutical name	Botanical name	Family	Major ingredients
Ophiopogon	*Tuber Ophiopogonis Japonici*	*Ophiopogon japonicus* Ker-Gawl.	Liliaceae	Ophiopogonin, ruscogenin, β-sitosterol, stigmasterol
American Ginseng	*Radix Panacis Quinquefolii*	*Panax quinquefolium* L.	Araliaceae	Saponins, panaquilon
Pinellia	*Tuber Pinellia, Rhizoma Pinellia Ternatae*	*Pinellia ternata* (Thunb.) Breitenbach	Araceae	Coniine, protoanemonin, homogentisic acid, nicotine, aspartic acid, glutamic acid, arginine, β-sitosterol, cholesterol
Raw Licorice	*Radix Glycyrrhizae Uralensis*	*Glycyrrhizae uralensis* Fisher	Leguminosae	Azetidine-2-carboxylic acid, aspartate, homoserine, diaminobutyric acid, digitalis glycoside
Lantern Tridax	*Herba Tridacis procumbentis*	*Tridax procumbens* Linn.	Compositae	Polysaccharide

standards. The placebo was prepared and encapsulated to taste, smell, and look similar to the mMMDT. Each capsule weighed 400 mg. A blinded primary research assistant managed all the questionnaires and was responsible for providing the capsules to the patients. All patients were treated in an equivalent fashion.

Record of symptoms

The patients were issued a diary card and asked to make twice daily entries of albuterol usage, and the severity of symptoms, if any. A 4-point scale was used to assess the extent of cough, wheeze, and breathlessness, with the score indicating the absence of symptoms, and mild, moderate, and severe symptoms, respectively; maximum possible total score was 9.

Determination of allergen-specific IgE antibodies

The amount of total and *Dermatophagoides pteronyssinus* (Dp)-specific IgE was determined using ELISA. Protein high-binding plates were coated with 100 μl of purified allergen or recombinant mouse anti-human IgE diluted in coating buffer (0.1 M NaHCO3; pH 8.2) to a concentration of 5 μg/ml. After overnight incubation at 4°C, plates were washed three times and blocked with 3% (wt/vol) BSA-PBS buffer for 2 h at 25°C. Sera were used at 1:10 dilution, with duplicate measurement. After overnight incubation at 4°C, biotin-conjugated mouse anti-human IgE mAb, diluted in 0.05% gelatin buffer, was added for an additional hour. Avidin-alkaline phosphatase (1:1000; Sigma Chemical Co., St Louis, MO, USA) was then added and incubated for 1 h at 25°C, followed by six washes. The color reaction was developed with the addition of the phosphatase substrate, p-nitrophenyl phosphate, disodium (Sigma Chemical Co.). Readings were referenced to a standard serum pooled from five patients who were newly diagnosed and had high IgE titers. The standard serum was calculated as 100 ELISA units/ml.

Statistical analysis

The primary outcome measure was percentage change in FEV_1 from baseline at each measured time point following treatment. Secondary outcome measures included asthma symptom score, and changes in total and specific IgE. A sample size of 100 patients provided sufficient power (90%) to detect a difference of a 10% difference in FEV_1 between treatment and placebo groups ($\alpha = 0.05$). Nonparametric statistics were used to determine p-values for group comparisons for all outcome measures. All reported p-values are two-sided and calculated using Prism software. Symptom scores are expressed as median with range. Serum total and allergen-specific IgE are expressed as mean ± SE. Wilcoxon's signed-rank and Mann–Whitney *U*-tests were used for intra- and inter-group analysis, respectively.

Table 2. Demographics, baseline characteristics and reasons for patient withdrawal

	Mai-Men-Dong-Tang			
	800 mg	400 mg	Placebo	p-value
No.	40	40	20	
Age (yr)	13.9 ± 10.5 (6–55)	14.3 ± 9.6 (5–47)	16.5 ± 10.6 (7–38)	0.696
Sex (male %)	19/14 (57.58%)	19/10 (65.52%)	13/4 (76.47%)	0.413
Height (cm)	138.0 ± 16.9 (109–177)	143.2 ± 19.1 (109–180)	144.0 ± 16.5 (116–169)	0.393
Weight (kg)	39.2 ± 18.7 (20–83)	40.5 ± 19.2 (16.6–84)	42.7 ± 15.7 (23–69.10)	0.807
AAS score	3.6 ± 1.3	2.93 ± 1.51	3.4 ± 1.4	0.199
Completed study, n (%)	33 (82.50)	29 (72.50)	17 (85.00)	
Reason for withdrawal, n				
Non-compliance with study drug	0	0	0	
Adverse effect of study drug	0	0	0	
Lack of benefit from study drug	1	2	2	
Medical condition other than asthma	1	3	0	
Moved from area	1	0	0	
Administrative reasons	4	6	1	

Table 3. Clinical assessments of therapeutic efficacy

	Mai-Men-Dong-Tang								
	800 mg			400 mg			Placebo		
Group	Before	After	p-value	Before	After	p-value	Before	After	p-value
FEV_1 (%)	71.7 ± 12.4	87.7 ± 12.6	0.009*	64.6 ± 9.7	73.8 ± 12.4	0.000*	75.3 ± 11.1	70.2 ± 13.7	0.097
Total IgE (IU/ml)	1399.4 ± 153.7	1174.3 ± 119.8	0.108	1266.3 ± 128.1	1222.9 ± 128.0	0.569	1215.9 ± 182.5	1131.7 ± 167.7	0.211
Dp-specific IgE (ELISA units)	68.0 ± 23.1	55.0 ± 7.5	0.517	101.5 ± 29.3	101.8 ± 11.2	0.751	80.9 ± 28.5	125.9 ± 34.6	0.121
IgG4 (ELISA units)	88.3 ± 39.6	81.8 ± 37.8	0.586	90.6 ± 29.3	89.00 ± 28.5	0.682	81.2 ± 33.1	79.3 ± 41.6	0.569
Symptom score	20.0 ± 31.2	10.8 ± 14.9	0.038*	43.9 ± 50.4	15.6 ± 21.8	0.041*	20.2 ± 21.1	12.6 ± 14.8	0.357

* indicates $p < 0.05$.

Results

Patients

A total of 100 patients were enrolled in this study and randomized into three treatment groups (40 patients in each mMMDT group and 20 controls) with similar patient demographics and baseline characteristics (Table 2). The AAS score was used to represent asthma severity, with no statistically significant between-group differences. Approximately 80% of the patients completed the study. Withdrawals included seven of 40 (17.5%) patients from the 800-mg mMMDT group, 11 of 40 (27.5) from the 400-mg mMMDT group, and three of 20 (15%) from the placebo group (Table 2). Reasons for withdrawal were similar across treatment groups. There was no patient withdrawal due to adverse effects.

Efficacy

After 4 months of treatment, significant improvements in lung function were achieved for both the 800-mg and 400-mg mMMDT groups, but not for the placebo group. The mean PEF values for the 800-mg mMMDT group were 63.17 ± 17.64% and 72.36 ± 20.81% before and after treatment, respectively ($p < 0.05$; Wilcoxon's signed-rank test). The PEF also improved from 46.76 ± 16.99% ($p < 0.001$) in the 400-mg mMMDT group. Mean FEV_1 also improved for the 800-mg and 400-mg treatment groups from 77.66 ± 12.43% to 77.73 ± 12.62%, and from 64.62 ± 9.72% to 73.76 ± 12.43%, respectively. The symptom score for the 400-mg group decreased from 43.93 ± 50.38% to 15.64 ± 21.81% ($p < 0.05$; Table 3). Further lung function improvement was observed over time for both mMMDT groups (Fig. 1), with the majority of patients showing an improvement of more than 10 compared with baseline (Fig. 2). The serum total IgE and Dp-specific IgE levels for the 800-mg mMMDT groups showed a decreasing tendency after treatment, however, no statistically significant difference was demonstrated, apparently due to the wide data distribution. The serum IgG4 for all three groups did not change in spite of treatment (Table 3).

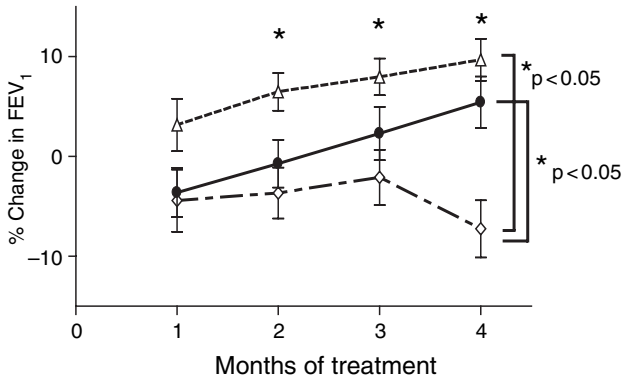

Fig. 1. Percentage change in FEV_1 from baseline after Mai-Men-Dong-Tang treatment over time. Data shown are mean ± s.d. Changes in FEV_1 were measured as described in Materials and methods. Patients receiving 400 and 800 mg/10 kg/day of mMMDT and placebo are depicted by lines marked with triangle, solid circle and square, respectively; * indicates $p < 0.05$.

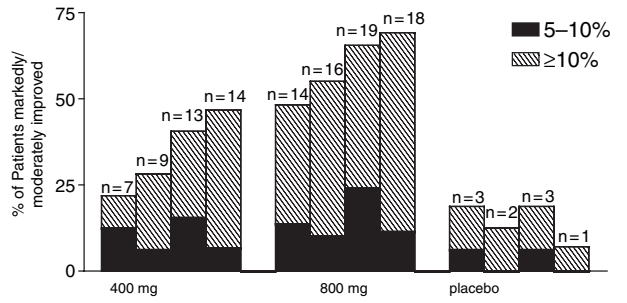

Fig. 2. Magnitude of improvement in FEV_1 from baseline after Mai-Men-Dong-Tang treatment. Solid bar indicates FEV_1 improvement of 5–10%; blank bar indicates FEV_1 improvement of over 10%.

Safety

Adverse effects were reviewed by investigators during each visit. No patient experienced a serious adverse event during treatment. All laboratory measurement values obtained during the study, including liver, kidney function and blood tests, were within normal reference values, with no significant differences demonstrated relative to the placebo-treated patients (Table 4).

Discussion

Recently, the usage of complementary preparations for asthma, especially herbal medicine, has prevailed (6–9). Nevertheless, lack of blinding, description of adverse effects, and withdrawal rates are frequent limitations to a number of randomized clinical trials investigating these herbal medicinal products. In addition, outcome measures are variable and, in several cases, of doubtful relevance (10). Therefore, we designed this randomized, placebo-controlled, double-blind study to investigate the efficacy and safety of the modified herbal formula, Mei-Man-Do-Tan (mMMDT), for the treatment of mild-to-moderate persistent asthma. MMDT was originally formulated by Zhang Zhong-Jjing, an outstanding physician who lived during the Han Dynasty (150–219 AD). Traditionally, practitioners of Chinese medicine believed that MMDT could treat various lung disorders, especially bronchial asthma. Although its pharmacological action has not been fully clarified, for centuries it has been widely prescribed, marketed and used to treat chronic lung disorders.

The modified MMDT consists of five herbs, ophiopogon, pinellia, licorice, American ginseng, and Lantern Tridax. In our previous animal study, the mMMDT decoction significantly decreased serum total IgE and house dust mite-specific IgE, and downregulated the expression of the IL-4 gene in allergen-sensitized mice (5). Therefore, we considered that mMMDT was a good candidate for a new treatment regimen for allergic asthma. We studied changes in FEV_1 as the first efficacy end point on account of their validity for monitoring of airway obstruction. By the end of the study, FEV_1 was significantly

Table 4. Laboratory assessments for safety by treatment group

	Mai-Men-Dong-Tang				Placebo	
	800 mg		400 mg			
	Before	After	Before	After	Before	After
WBC	7957.6 ± 1735.3	7946.9 ± 1999.4	8064.0 ± 2765.5	6982.6 ± 2291.9	7887.5 ± 1782.5	7176.9 ± 1238.4
Hb	12.7 ± 0.7	13.0 ± 1.1	13.5 ± 1.0	13.4 ± 1.1	13.1 ± 1.3	13.4 ± 1.4
Creatinine	0.7 ± 0.2	0.7 ± 0.1	0.5 ± 0.2	0.7 ± 0.2	0.7 ± 0.1	0.7 ± 0.1
BUN	13.2 ± 3.2	12.9 ± 3.0	12.9 ± 3.8	13.6 ± 3.2	13.2 ± 4.2	15.1 ± 4.2
GOT	18.6 ± 4.0	18.5 ± 4.8	18.1 ± 2.7	21.3 ± 4.6	19.0 ± 5.5	20.5 ± 8.0
GPT	12.9 ± 6.6	13.0 ± 7.9	14.4 ± 7.9	17.4 ± 13.6	16.3 ± 15.8	18.4 ± 13.8
Weight (kg)	39.6 ± 18.7	40.2 ± 17.7	40.5 ± 19.2	41.9 ± 18.5	42.7 ± 15.7	43.8 ± 15.9
Height (cm)	138.0 ± 16.9	138.1 ± 25.2	143.2 ± 19.1	144.6 ± 18.6	144.1 ± 16.5	146.3 ± 16.8

improved in both groups of mMMDT-treated patients (Table 4). Moreover, a marked progression in lung function of more than 10 compared with baseline was achieved for most patients (Fig. 2). Importantly given the therapeutic emphasis on symptom relief, the severity of problems including, coughing, wheezing, and breathlessness was alleviated in both mMMDT-treatment groups. The serum total IgE for the treatment groups showed a decreasing tendency after treatment but statistical difference was not noted. That was apparently due to the wide data distribution. In addition, the treatment was quite safe in our sample population, with neither severe side effects nor adverse events noted over the 4-month treatment period.

Previous studies have shown that glycyrrhizin or glycyrrhetinic acid of licorice can influence steroid metabolism (11). Additionally, immunomodulating effects have been demonstrated for the extract of American Ginseng, especially in terms of secretion of tumor necrosis factor alpha (12). Ophiopogon contains substantial quantities of isoflavonoids, which possess anti-inflammatory, antiallergic, antihistaminic and angioprotective properties, as well as potent phosphodierterase inhibitors (13). However, our previous animal studies have demonstrated that individual herbs could not downregulate IgE synthesis or improve lung function in murine models (unpublished data). On the basis of the results of this study, however, it seems reasonable to suggest that the combination of these five herbs may improve lung function and ameliorate clinical symptoms. The original Chinese herbal formulation was typically composed of at least four different ingredients. As well as reducing the possible side effects caused by one or more of the herbs in the formula, these combinations frequently exhibit a therapeutic synergy (14, 15). Thus, further research is needed to clarify the mechanisms that underlie these synergistic effects. In conclusion, the results of our investigation suggest that due to its efficacy, safety, low cost and favorable compliance characteristics, mMMDT can be considered an effective treatment regimen for persistent, mild-to-moderate asthma in addition to current therapies.

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