

Clinical Report 3

Immediate Effects of Maoto in Pediatric Patients with Nasal Obstruction

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Introduction

Maoto (Ma huang tang) is a prescription listed in the Chinese medical classic Shang Han Lun¹⁾, written in AD 219 by (Zhang) Zhong jing and contains the following galenicals: *Ephedrae* Herba, *Armeniacae* Semen, *Cinnamomi* Cortex, *Glycyrrhizae* Radix. The main ingredient *Ephedrae* Herba is known as the ideal plant type for ephedrine. *maoto* has been used since ancient times for the treatment of patients complaining of nasal obstruction, sneezing, running nose, cough, chills, fever, headache, arthralgia etc. as early symptoms of colds. It has been handed down by word of mouth, that it provides in particular in infants with nasal obstruction quick relief, but so far no objective results supporting this assertion have been provided.

In the present study the author used acoustic rhinometry²⁾, allowing non-invasive, highly accurate, geometric measurements of the nasal cavity almost without the necessity for cooperation by the examinee and a visual analogue scale^{3,4)} that can be applied to a variety of subjective, sensory measurements to evaluate the immediate effects of *maoto* on the form of the nasal cavity and feeling of nasal obstruction in pediatric patients with allergic rhinitis.

Here I am going to report the results of the study, showing as handed down, that *maoto* has immediate effects, relieving nasal obstruction both subjectively as well as objectively.

Subjects and methods

I. Subjects included in the study

The study included patients, who had been visiting the department of otolaryngology of the Daitai Welfare Hospital or the Matsuzaka Central Hospital between March 8, 2006 and March 7, 2007 and in whom interviews, rhinoscopies, examinations of the rhinal

discharge for eosinophils, tests for total serum IgE value and specific IgE antibodies were performed according to the "Practical guidelines for the management of allergic rhinitis in Japan <PG-MARJ>" and in this way diagnosed either with perennial or seasonal allergic rhinitis. The purpose of the clinical study was sufficiently explained to both the pediatric patients and their guardians and based on their consent, 25 patients (14 boys, 11 girls, age distribution 5.6 to 14.9 years, average \pm standard deviation 9.6 \pm 2.8 years, duration since onset: 0.7–108 months, average \pm standard deviation 45.3 \pm 31.6 months) served as subjects.

Nineteen cases were considered to be perennial allergic rhinitis due to house dust and included 4 cases complicated by cryptomeria pollinosis. Two patients suffered from cryptomeria pollinosis and in the remaining 4 patients had antigens that could not be identified.

Fourteen of the patients had a history of complications of bacterial infection induced nasal and paranasal sinusitis, 6 patients had exudative otitis media, 6 patients had bronchial asthma and 4 patients had a history of atopic dermatitis.

The subjects did not receive any treatments that might have influenced the evaluation of the effects, at least not within one week prior to trial begin.

Oriental medical findings:

The diagnosis was made based on the diagnostic criteria of Terazawa⁶⁾, taking yin-yang, the physical constitution, deficiency-excess, heat-cold and qi/blood/water anomalies into account. Regarding yin-yang balance there were no patients with a clearly yin or clearly yang dominated condition. As viewed from the physical constitution too there were no obvious cases of excess, but 4 patients were considered to have a deficiency condition. Regarding the heat-cold duality 13 patients were considered to have heat conditions, 4 had cold conditions and 8 had neither. Regarding qi-blood-water, conditions were somewhat overlapping, but 6 patients had apparently qi

deficiencies, 3 qi reversal, 6 qi depression, 8 blood deficiency and 6 patients had water retention syndromes.

II. Test drugs and dosages

The test drug Tsumura *maoto* extract (TJ-27, 2.5 g per package, containing in 7.5 g the amount of 1.75 g dry crude drug extract, composed at a ratio of Mao=5.0, Kyonin=4.0, Keihi=3.0, Kanzo=1.5) was used. The size of individual doses (5-7 years = 1/2 package, over 12 years or a body weight of more than 45 kg = 1 package each) were calculated depending on age and body weight and each single dose was administered dissolved in 100 ml of warm water.

III. Evaluation of the nasal obstruction

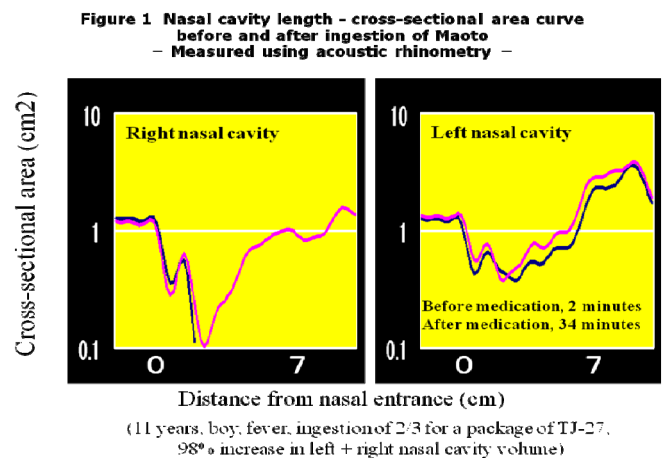
1) A face visual analogue scale (F-VAS) was used for the subjective evaluation of the feeling of nasal obstruction

To express the degree of distress in steps, a 100 mm long horizontal bar with 5 different faces along its length was used to evaluate the feeling of nasal obstruction before and after ingestion of TJ-27. The F-VAS had short vertical lines at both of its ends, where the left end represented a degree of 0 (no feeling of nasal obstruction at all, capability of breathing through both nostrils with closed mouth), while its right end represented a degree of 100 (had to use mouth breathing, since with closed mouth breathing through both nostrils was impossible).

The meaning of the F-VAS was explained to the affected children, so that they could mark the intensity of the feeling of nasal obstruction before and after ingestion of TJ-27 at that point of time. Moreover, the distance from the left end to the marked position was measured. The VAS score was obtained by assigning a value of 1 to each 1 mm. Accordingly, the VAS-score of the feeling of nasal obstruction had a distribution range of 0-100, where higher values indicated a stronger degree of the feeling of nasal obstruction.

2) Application of acoustic rhinometry (AR) to the objective evaluation of the form of the nasal cavity

AR employs sound reflections to measure the geometrical form of the nasal cavity. An incident beam of sounds generated by a sound generator are directed through a wave tube of suitable size selected according to the size of the examinees anterior nares and fitted to these via a nose piece and thus into the nostrils. A portion of these sound waves alter the acoustic impedance of the various structures in the nasal cavity and are then reflected back into the wave tubes. The temporal and spatial correlation between the incident and reflected waves are recorded with a microphone installed inside the wave tubes. Subsequent computer analysis then reveals the distances from the anterior nares to the various structures in the nasal cavity, which are then used to plot the cross-sectional area in form of a cross-sectional area – distance curve (Figure 1). Moreover, integration allows to calculate the volume of any arbitrary range of the nasal cavity²⁾.



For the present study I used a device manufactured at the Aarhus University, Research Laboratory for Environmental and Occupational Medicine (most of the parts have been gathered and stored by GJ Elektronik, Skanderborg, Denmark, so that I used the computer program NADAP) and with this objectively evaluated the nasal obstruction before and after administration of TJ-27. In the present research I used pediatric nose pieces with an internal diameter of 7 mm for the anterior nares.

The examination was carried out in the order right nose -> left nose and the base line of the cross-sectional

area – distance curve formed by the nose piece section was horizontal, so that abnormal increases were considered to be indicative of sound leakage at the nose entrance, or inappropriate angle of insertion of the nose piece, resulting in abnormal decreases. After confirmation that no such anomalies were present and of the reproducibility, data were gathered, stored and used as material for the analysis.

A calculation program (RHINO) was used to calculate the minimum cross-sectional area (MCA) for the left and right nasal cavities as well as their respective nasal cavity volumes (NCV) as parameters for the nasal obstruction. During the calculation of the nasal cavity volume the distance from the front end of the nasal cavity to its back end (nasal cavity length) was sought, but for the present study I referred to the results of previous investigations and calculated this parameter according to the equation "nasal cavity length" (mm) = 40.6 + 1.07 x age (years), entering here the age of the pediatric patient.

IV. Objective evaluation of the taste of *maoto*

The same 100 mm horizontal F-VAS used for the evaluation of the feeling of nasal obstruction was also used to evaluate the taste of TJ-27 immediately after the children had taken the drug. Here too the left end was defined as representing a degree of 0 (best possible taste), while its right end represented a degree of 100 (worst possible taste). Accordingly, the VAS-taste score too had a distribution range between 0 and 100, where increasing values indicated increasingly worse taste.

V. Progression of the clinical research

The VAS for the feeling of nasal obstruction, MCA and NCV were measured between 1 and 13 minutes prior to the ingestion of TJ-27. The taste-VAS was measured immediately after the ingestion of TJ-27 and between 28 and 60 minutes later the VAS score for the feeling of nasal obstruction, MCA and NCV values were remeasured.

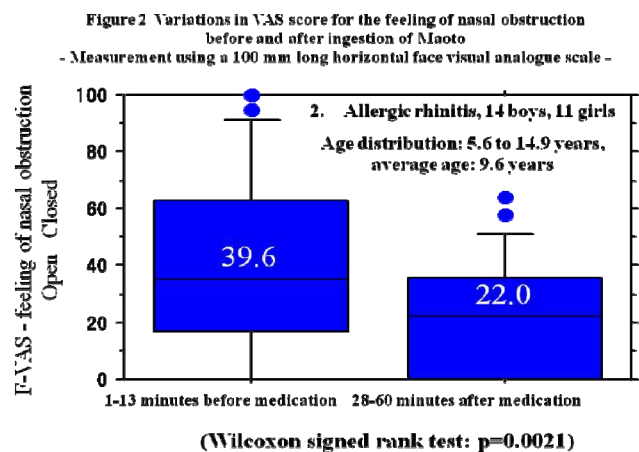
VI. Statistical examination

The computer program StatView 4.0 (product "Abacus Concepts") was used and the two groups compared using a method suited for the examination of ordinal variables, for which a sufficient normality cannot be obtained (Wilcoxon signed rank test, Spearman rank correlation) and subsequently the relevant correlations examined. The results showed a statistically significant difference of $p < 0.05$.

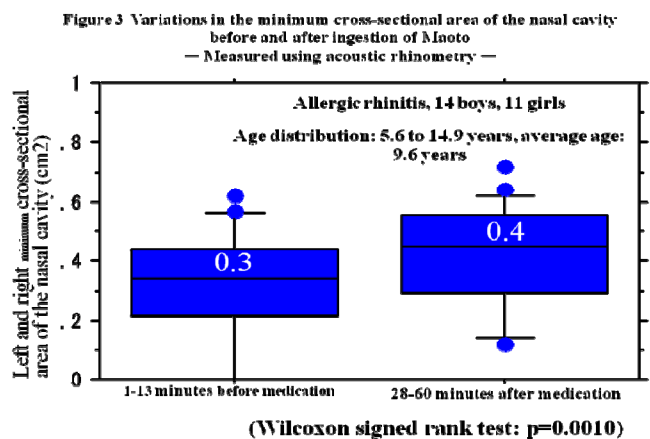
Results

1) Variations in VAS score for the feeling of nasal obstruction (Figure 2)

The "Before" value of the VAS score of the feeling of nasal obstruction had a 0-100 distribution and an average \pm standard deviation range of 39.6 ± 6.0 . The "After" value decreased to a 0-64 distribution and 22.0 ± 4.1 , showing a significant difference between the two values ($p = 0.0021$).



2) Variations in the MCA before and after ingestion of *maoto* (Figure 3)

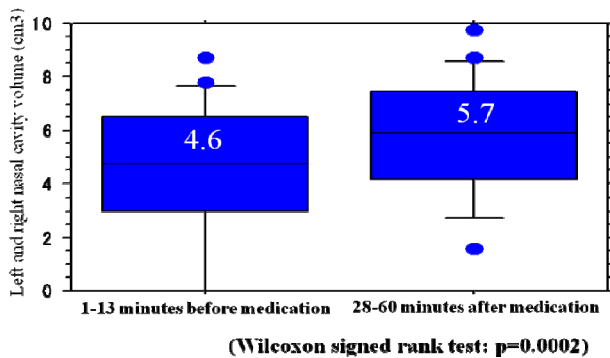


The "Before" value of the MCA had a 0-0.62 cm² distribution and an average \pm standard deviation range of 0.32 \pm 0.04 cm². The "After" value of the MCA increased to a 0-0.72 cm² distribution and an average \pm standard deviation range of 0.41 \pm 0.04 cm². There was a significant difference between the two groups ($p=0.0010$).

3) Variations in the NCV before and after ingestion of *Maoto* (Figure 4)

The "Before" value of the NCV had a 0-8.77 cm³ distribution and an average \pm standard deviation range of 4.56 \pm 0.51 cm³. The "After" value of the NCV had a 0-9.79 cm³ distribution and the average \pm standard deviation range increased to 5.68 \pm 0.48 cm³. There was a significant difference between the two groups ($p=0.0002$). The increase in NCV being greater than 15% was considered to show for 40% of the patients (10/25) objectively, that *maoto* had an effect countering the nasal obstruction.

Figure-4 Variations in the nasal cavity volume before and after ingestion of *Maoto*
— Measured using acoustic rhinometry —
(Allergic rhinitis, 14 boys, 11 girls; age distribution: 5.6 to 14.9 years; average age: 9.6 years)



4) Taste-VAS score

The taste-VAS score had a 0-100 distribution and an average \pm standard deviation range of 52.2 \pm 6.5. The taste of *maoto* was found to be rather acceptable, since the ratio of taste-VAS scores below 50 was 52%.

5) Correlation between the taste-VAS score and the increase in NCV

There was a significant correlation ($\rho= -0.173$, $p=0.3962$) between the taste-VAS score and the increase in NCV.

6) Correlation between subjective feeling of nasal

obstruction and objective verification via the form of the nasal cavity

Between the decrease in the subjective VAS score for the feeling of nasal obstruction and the increase in the objectively measured NCV there was a statistically significant correlation ($\rho= -0.266$, $p=0.1918$). Yet, subtraction of the VAS score for the feeling of nasal obstruction after the drug administration from the VAS score for the feeling of nasal obstruction obtained prior to the medication, in other words, the subjectively felt reduction of the nasal obstruction, suggested that there was a correlation to the value of the NCV prior to the drug administration subtracted from the NCV value after the medication, in other words, the objectively measured increase in the NCV ($\rho=0.327$, $p=0.1107$).

7) Adverse reaction did not occur during this clinical research.

Discussion

Maoto is one of the prescriptions listed in "Shang Han Lun" and contains the following galenicals: *Ephedrae* Herba, *Armeniacae* Semen, *Cinnamomi* Cortex, *Glycyrrhizae* Radix.

Among the ingredients extracted from *Ephedrae* Herba ephedrine has been most thoroughly researched. It has an adrenaline like, sympathomimetic action, causes in small doses dilation of the pupils, in large doses generalized paralysis, increases blood pressure, promotes sweating and relaxation of the bronchi. Also, in a similar way the pseudoephedrine extracted from *Ephedrae* Herba dilates the renal blood vessels and has diuretic actions.

Cinnamomi Cortex has, according to Kampo medical pharmaceutical principles, body warming, sudatory and dispersing actions, at the same time it is fortifying the stomach and thus a compound of many Kampo prescriptions.

Glycyrrhizae Radix has in Kampo medicine a relaxing, mitigating action and is said to be thirst quenching and is compounded in many Kampo prescriptions to soften and adjust the actions of the various component crude drugs. For this reason it is considered to be one of the most basic galenicals in

Kampo medicine and is also been called "key retainer". From a western medical point of view it has detoxifying, antispasmodic, expectorant, anti-anaphylactic, anti-inflammatory and similar actions and glycyrrhizin is a well known constituent widely used in western medical settings as a drug both for internal use as well as in preparations for infusion. Hypokalemia and edema have been indicated as possible side effects of glycyrrhizin, so that both single large doses and prolonged use of small doses too should be avoided. *Armeniacae* Semen is in Kampo prescriptions often combined with *Ephedrae* Herba and has antitussive and expectorant effects.

Maoto is used, based on experience, during the early stages of the common cold for symptoms like headache, chills, fever, low back pain, cough, asthma and the like, and regarding pediatric patients it has been widely spread by word of mouth, that it is extremely effective in relieving nasal obstruction.

Keiichi Ichimura⁸⁾ noted in his introduction to the treatment of nasal obstruction, that *maoto* would be the drug of first choice during the treatment of nasal obstruction in infants. The reasons are (1) *maoto* definitely improves the nasal obstruction, (2) the vasoconstrictive actions of ephedrine hydrochloride of drugs for internal use require care and thus should be used cautiously, (3) the vasoconstrictive actions of nasal drops are stimulants for α -adrenergic receptors and thus have powerful actions taking effect immediately, but the infection induced tissue edema resulting in the nasal obstruction cannot be completely relieved through the vasoconstrictive actions. He also stated, that in infants stimulation of central α_2 -receptors is contraindicated because of the respiratory and circulatory depression as well as the development of lethargy, this could easily induce.

Makoto Arai et al.⁹⁾ reported one case of a 4-year old boy, in whom *maoto* was effective for nasal obstruction and snoring. The results of a search of the available literature are described below. The number of reports describing the treatment of nasal obstruction with *maoto* is surprisingly low, but already a long time ago Yodo Odai wrote in the headnotes for *maoto* in his Ruiju-ho-kougi "This prescription gives immediate relief in cases, when newborn babies develop a fever,

development of nasal obstructed blocking the passage of the nose, so that the infant cannot suckle."

In this way *maoto*, from a modern medical point of view too, has been recognized as being useful for the treatment of nasal obstruction, but so far objective evidence for the effectivity of *maoto* using western medical methods has not yet been presented.

The author investigated in the present study with western medical methods whether *maoto*, randomly administered to infants with nasal obstruction, has any immediate effects and if it does, the degree of these effects. The results definitely showed a significant relief of the subjective feeling of nasal obstruction following the administration of *maoto* ($p=0.0021$) and a significant increase in the MCA, which served as a parameter for the intensity of the feeling of nasal obstruction ($p=0.0010$). Without contradicting these results the NCV also increased significantly following the administration of *maoto* ($p=0.0002$) and the observed magnitude of this increase of more than 15% revealed, that *maoto* had in 40% of the cases (10/25) a clear effect opposing the nasal obstruction. These results objectively verify the Kampo medical tradition handed down by word of mouth, that "*maoto* has immediate effects relieving nasal obstruction in infants".

In general, Kampo medicine tastes bad, but *maoto* has been rated as tasting rather good by 52% of the patients. This gives the Kampo administered to infants a generally satisfactory taste. Yet, compared to western medicine Kampo medicine still has the disadvantage of tasting bad and being difficult to swallow. In Kampo medicine the tradition holds, that if a patients finds the medicine tasting good, there is a high likelihood of that medicine having a good effect in the particular patient. The affected infants serving as subjects for this study indicated, that there was no significant correlation between the taste, as evaluated using a VAS and the increase in NCV ($\rho = -0.173$, $p=0.3962$), but when the score of VAS for nasal obstruction obtained after the administration was subtracted from the same score obtained prior to the medication, in other words, the degree of the decrease in the feeling of nasal obstruction tended to correlate with the NCV value prior to medication subtracted

from the NCV value obtained after the drug administration, i.e., the degree of increase in NCV. Yet, this could not yet be called a statistically significant correlation ($p=0.327$, $p=0.1107$). A VAS is clearly a scale used for subjective evaluation and thus characterized by large individual variations. For example, a score of 40 for the feeling of nasal obstruction in one affected infant may have a vastly different meaning from the same score of 40 in a different pediatric patient. Thus, when the VAS score for the feeling of nasal obstruction was frequently measured in a particular affected child, this correlated well with the simultaneously and with the same frequency performed measurements of the NCV. Yet, as in the present study, when these measurements were made only once or twice in a group of several pediatric patients, there was almost no correlation between the two measurements¹⁰. Consequently, the results of the present study had been anticipated, but it should be noted, that there is tendency towards a correlation.

Conclusion

A total of 25 pediatric patients (14 boys, 11 girls, age distribution 5.6 to 14.9 years, average \pm standard deviation range 9.6 \pm 2.8 years, duration since onset: 0.7–108 months, average \pm standard deviation range 45.3 \pm 31.6 months) diagnosed either with perennial or seasonal allergic rhinitis was treated with the usual dose of *maoto* extract granules as single doses, using a face visual analogue scale and acoustic rhinometry (AR) between 28 and 60 minutes after the medication to evaluate its immediate effects. The results showed a significant, subjective reduction of the feeling of nasal obstruction ($p=0.0021$) and a significant increase in the MCA and NCV, serving as objective parameters of the nasal obstruction ($p=0.0010$ and $p=0.0002$). The increase in NCV being greater than 15% was considered to objectively verify, that *maoto* had an effect countering nasal obstruction in 40% of the patients (10/25). Adverse reactions did not occur during this clinical research.

In Kampo medicine *maoto* is used during the early stages of the common cold for symptoms like headache, chills, fever, low back pain, arthralgia, cough, asthma and the like and is said to be extremely effective in particularly for relieving nasal obstruction in pediatric

patients. The present study objectively verified, that this is true and *maoto* can be ranked even in a modern medical setting as an extremely useful medication for the treatment of nasal obstruction in pediatric patients.

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