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Original Article

Rapid improvement of respiratory quality in asthmatic children after "assisted drainage" therapy

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Abstract

Introduction Whilst current asthma management is well-developed, there are still 5-10% uncontrolled asthma patients with unknown etiologies. However, its connection with oral focal infection is still uncertain. Therefore, a collaborated research for asthma management was conducted by pediatricians and dental practitioners. Within minutes after the "assisted drainage" therapy, a modification of scaling root planning procedure, there is rapid improvement of respiratory function, i.e., forced expiratory volume one second (FEV1) in asthmatic children. This quick response usually achieved by oral inhalation.

Objective To investigate the effectiveness of the assisted drainage therapy in the improvement of respiratory quality.

Methods Fifteen asthmatic children were subjected to a longitudinal study for two weeks. In the first week they were instructed for allergen avoidance only and the following one week was combined with the assisted drainage therapy, followed by dental health education and dental plaque control therapy. Each subject was assessed for respiratory quality with a computerized spirometer and blood sampling test. Paired t-test analysis was used for statistical analysis.

Results Assisted drainage therapy was performed, within minutes FEV1 increased significantly (P= 0.001). Additionally, there were significant differences serum histamine (P= 0,001) pre and post treatment.

Conclusions The assisted drainage therapy is effective as an adjuvant therapy for mild persistent asthma in children. **[Paediatr Indones. 2010;50:199-206]**.

Keywords: *assisted drainage therapy, respiratory quality, adjuvant therapy, allergic asthma, children*

Asthma prevalence of all ages throughout the world is increasing, including in Indonesia. Epidemiological studies during 1991-2003 in Indonesian children (6-15 years) revealed variable results, from 2.6% in Bandung (1997) up to 17.4% in Jakarta (1996).[1] Approximately two-thirds of asthma is allergic and >50% of patients with severe asthma have allergic asthma. Allergic asthma or immunoglobulin E (IgE) mediated asthma is characterized by the presence of IgE antibodies against one or more common environmental allergens. Asthma can be controlled by taking bronchodilators or corticosteroids, mast cell stabilizers, food and environmental allergen avoidance, immunotherapy, etc. Nevertheless, there are still 5-10% patients who unsuccessfully controlled.[2] In addition, some etiologies of asthma were still unknown;[3] therefore, other possibility such as oral focal infection as a trigger of asthma co-morbidities (i.e. rhinosinusitis)[4,5] should be considered.

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Although asthma management has been updated every year, until the beginning of 2009 control of oral infection was not included in asthma management protocol.[6,7] It could be related to an established concept by David Strachan with a catchy name the "hygiene hypothesis". It proposes that early infections may enhance the T-helper 1 (Th1) immune response development which is allergy-resistant.[8] This concept is also adopted by dental researchers.[9,10] On the other hand some believe that dental treatment increases anxiety which trigger asthma exacerbation.[11] Therefore, the concept of reducing asthmatic symptoms through elimination of oral infection is not easily accepted either by medical or dental professionals.

Several case reports revealed that asthmatic symptoms could be diminished by elimination of oral infection[12] and dental plaque control therapy.[13] In addition, rapid resolution of rhinosinusitis, one of asthma co-morbidities, is reported after intraoral approach that proposed as the "assisted drainage" therapy.[14] However, the evaluation was only based on the subjective symptoms and did not collaborate with competent physician. In this study, asthma management was done by dental practitioners in collaboration with pediatricians and pediatric allergy consultant in Department of Child Health Dr. Soetomo Hospital, Surabaya. Evaluation of respiratory quality for forced expiratory volume in one second (FEV1) was done using a computerized spirometer (Vitalograph Spirotrac IV).[15] It was interesting that the assisted drainage therapy was able to increase FEV1 within minutes; this quick response actually resulted from β-adrenergic inhaler. However, it could be elucidated with several theories: the neurogenic switching mechanism[16] and the axon reflex (i.e. nasobronchial reflex).[17] We aimed to evaluate the effectiveness of the assisted drainage therapy on the improvement of FEV1 and serum histamine level, and tried to elucidate the possible mechanism how this therapy may able to increase the FEV1 in minutes.

Methods

Design

This study was conducted in the Allergy Immunology Outpatient Clinic, Department of Child Health, Dr. Soetomo Hospital Surabaya during July-September 2007. The study protocol was reviewed and approved by the Medical Research Ethical Committee of Dr. Soetomo Hospital. The study was done by two pediatricians and two dental practitioners.

We included 6-11 year-old children who matched the screening criteria on visit 1: (1) suffered from mild persistent asthma (symptoms > two times per week but < one time per day; exacerbations that may affect activity; nighttime asthma symptoms > two times per month) and criteria as determine by PNAA 2004 for ≥ three months were recruited; (2) qualified for a pre-bronchodilator forced expiratory volume in one second (FEV1) ≤ 75% of Polgar predicted normal value or had FEV1/FVC ratio < 80% (if FEV1 > 75%); (3) FEV reversibility criteria on the basis of an increase in FEV1 ≥ 12% from pre-bronchodilator FEV1, 15-30 minutes after two puffs of a salbutamol inhaler; (4) positive skin prick test for certain allergens (SPT); (5) dental plaque index (DPI) ≥ two using Silness and Loe scoring method; (6) blood sampling test revealed normal bleeding time and other contraindications for this study; (7) and intended to participate as indicate by a signed informed consent form by their parents.

We excluded subjects who: (1) had severe oral or dental lesions: deep caries, acute gingivitis, severe malocclusions, severe soft tissue ulcerations; (2) using orthodontic appliance or prosthesis; (3) any acute exacerbation of asthma; (4) clinically relevant mouth, throat, and upper respiratory infections within one month prior to visit 1; (5) had past or present specific diseases or disorders: hemostatic disorder, diabetes mellitus, congenital heart disease, rheumatic heart disease, hypertension, hepatitis, cirrhosis, tuberculosis, malignancy, HIV infection, convulsive disorder, mental retardation, ADHD, autism, obesity, and any medical conditions considered that may interfere or put subject at risk because of participating in the study; (6) using drugs or immunotherapy: antibiotics, oral or parenteral steroids, long acting β-agonist, anti-leukotriene modifiers, anticholinergics, xanthine, cromoline, or antihistamine during at least two weeks prior to Visit 1 or any time during the study; (7) any history of smoking (subjects, parent or others in the same house).[15]

Subjects were eliminated from this study at any time for specific reasons: (1) decrease in FEV1 ≥ 25% from visit 1 or < 40% of predicted; (2) had

acute exacerbation of asthma that need the use of asthma controller medication; (3) taken any form of medication that could affect their periodontal status, such as anti-inflammatory agents, antibiotics and immunosuppressant during the study period; (4) non-compliance with the oral hygiene maintenance and (5) rejecting for blood sampling procedures.[15]

Study protocol

We recruited subjects until the required sample size[18] was fulfilled. Each subject was initially assessed and scheduled for evaluation after one week run-in period. At each visit, dental plaque index, lung function test using computerized spirometry, and serum histamine level were measured. At Visit 1, the subjects were only told to avoid certain foods which suspected to be allergenic (food allergen avoidance) and other asthmatic exacerbation triggers (heavy exercise, cold weather).

Laboratory examination was done at the Hematology Division, Department of Child Health, and the Department of Clinical Pathology, Dr. Soetomo Hospital. Evaluation of serum histamine (2-[4-imidazole]-ethylamine) was chosen because it was an important inflammatory mediator, released in airways during an asthmatic response. Several effects of histamine in asthma pathogenesis were acute inflammation, smooth muscle contraction, edema, vasodilation, mucus hypersecretion, and adhesion molecule up-regulation. It also increased airway hyperresponsiveness and antigen uptake.[19] Serum histamine level was measured with histamine immunoassay method; lower value was more favorable (N=0-1 ng/ml). For additional information, histamine had degradation time in 4-8 hrs and half-life in 6.8-20.2 min (mean 11.5 min) in humans.[20]

At Visit 1, blood sampling procedures were done twice, 1st for screening purposes and 2nd after decided as inclusive samples. At Visit 2, blood sampling procedures also done twice, before and two hours after dental treatment; visit 3 was only once after lung function test.

Dental management

Dental management was done in Visit 2 after evaluation of oral hygiene and respiratory quality test. It was initiated with the "assisted drainage therapy" (ADT), a modification of the scaling root planning (SRP) method, conducted using a thin and small sickle shaped scaler. If it was not easily available, sickle shaped explorer could also be used. Before ADT, gingival sulcus was irrigated with hexetidine 0.1% (Hexadol®, Otto Pharm.) for one minute. Scaler was used for subgingival plaque removal, concomitantly combined with several strokes with its back surface (round shape) for massaging the surrounding gingival sulcus tissue with tender pressure for about 2-3 minutes per tooth **(Figure 1).** For asthma and its co-morbidities (sinusitis and rhinitis), surrounding gingival sulci of first permanent molars, second primary molars or second premolars were the sites of choice.[13,14]

Without anesthetics, this procedure should be done until blood "oozed" passively from the gingival sulcus tissue. It was important that this procedure should be done tenderly and does not elicit pain; therefore, the patient was told to give a signal such as raising his/her left hand if pain felt. Pain was an indicator of unintentionally stimulating the healthy gingiva, which was considered unnecessarily in this procedure. It answered the question why anesthetics should not be used in this procedure.

An important indicator for direct evaluation of the success of the ADT was the "paper blowing" test. It was done after about three minutes after the ADT by blowing a piece of paper with nose in the treated side, concomitantly with closing the mouth and the other nostril with the operator's finger. If the patient was able to blow the paper without effort, the procedure was successful. Subsequently, it was followed by dental health education (DHE) and dental plaque control therapy (DPCT) and also told to rinse with hexetidine 0.1% twice daily.

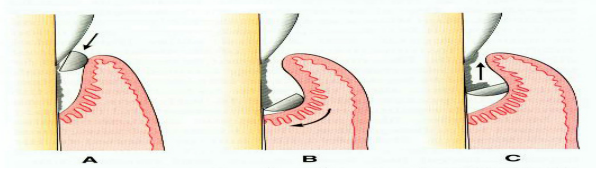

Figure 1.The assisted drainage therapy, scaling-root planing (SRP) plus gingival sulcus tissue massage using sickle shaped scaler (red arrow)

Allergen avoidance

The subject's parents or responsible persons were told to complete a detailed questionnaire regarding the characteristics and asthma history with questions concerning triggers, medication use, and other asthma-related variables. Subsequently, they were also informed how to facilitate allergen avoidance of various potentially allergenic foods, house dust and pet control.

Lung function test

Lung function test were performed by pediatrician at Visit 1 and Visit 2. In Visit 2, LFT (includes the FEV1) was done 5 minutes and 30 minutes consecutively after ADT. This study used a microprocessor-based electronic spirometer (Vitalograph Spirotrac IV) that displayed a spirogram as well as the lung function reading. It automatically generated subject's age, sex, race, height and weight into the predicted normal lung-function values based on the Polgar's regression equations and considered as the baseline standard for every subject. Spirometer was calibrated each day of the study to maintain quality control. The lung function test was conducted between 8 to 9 AM to standardize and related to circadian rhythm in asthmatic response. To ascertain reproducibility of spirometry results, at least three acceptable spirograms must be obtained. When a minimum of three tests are performed, the spirometer selected the best reading and calculated the predicted lung function value (%) for that reading. Higher value (%) means better FEV1 improvement.[15]

Statistical analysis

The paired t-test of the means before and after intervention was used to compare FEV values. The level of statistical significance was set at $P < 0.05$, and 95% confidence intervals were supplied where appropriate. SPSS package (version 11.00 for Windows) was used for data analysis.

Results

Among the 21 subjects with mild persistent asthmatic children qualified for the study, we randomly selected 15 for study. These 15 subjects had no differences in characteristics (duration of asthma, asthma triggers, allergy risk, skin prick test result), clinical history and initial laboratory results. Nine boys and six girls selected had mean age of 8.67 (SD 1.40) years. All variables had normal distribution according to the Kolmogorov-Smirnov test except for the gender variable ($P= 0.023$).

The FEV1 increased significantly after ADT had been done. Examination with computerized spirometer was done after 5 minutes and 30 minutes, both had significant difference results (**Table 1**) compared to allergen avoidance therapy only. This rapid increase of FEV1 value in minutes could only be achieved by bronchodilators (i.e., β2-agonist inhaler).

Statistical evaluation with t-test for paired samples showed that allergen avoidance only had significant difference with control ($P=0.006$). Nevertheless, higher value means that it had less pronounce ressult than allergen avoidance therapy (AAT) combined with ADT after 5 min ($P=0.001$), 30 min ($P=0.001$) and 1 week ($P=0.001$). The effectiveness of ADT was measured based on FEV1 change after AAT only vs. AAT with ADT after 5 min, 30 min and 1 week; all groups had significant difference ($P<0.05$) (**Table 2 and Figure 2**).

Regarding to allergic reaction which measured by serum histamine level, there was no significant difference found between control and AAT only

Table 1. Comparison between FEV1 samples (%) (paired t-test)

No	Variables	Mean	SD	P
1	Control vs. 1 week AAT	-5.3267	6.4182	0.006
2	1 week AAT vs. 5' after ADT	-9.1933	7.3537	0.001
3	1 week AAT vs. 30 minutes after ADT	-10.7000	8.33230	0.001
4	1 week AAT vs. 1 week after AAT + ADT, DPCT and DHE	-9.600	8.3543	0.001

Notes: Higher negative value indicates better improvement of respiratory quality based on FEV1; AAT= allergen avoidance therapy; ADT=assisted drainage therapy; DPCT= dental plaque control therapy; DHE= dental health education

(p=0.832). However, there was significant difference in serum histamine level AAT before and after ADT, after two hours (lag time between treatment and blood sampling procedures in one day) (P=0.001) and one week after conducting AAT combined with dental treatment (ADT and DPCT) and DHE (P=0.001) (**Table 3**).

The effectiveness of ADT was measured based on the serum histamine level change after AAT only *vs.* AAT with ADT after two hrs and one week; all groups had significant difference (P<0.05) (**Table 4 and Figure 3**).

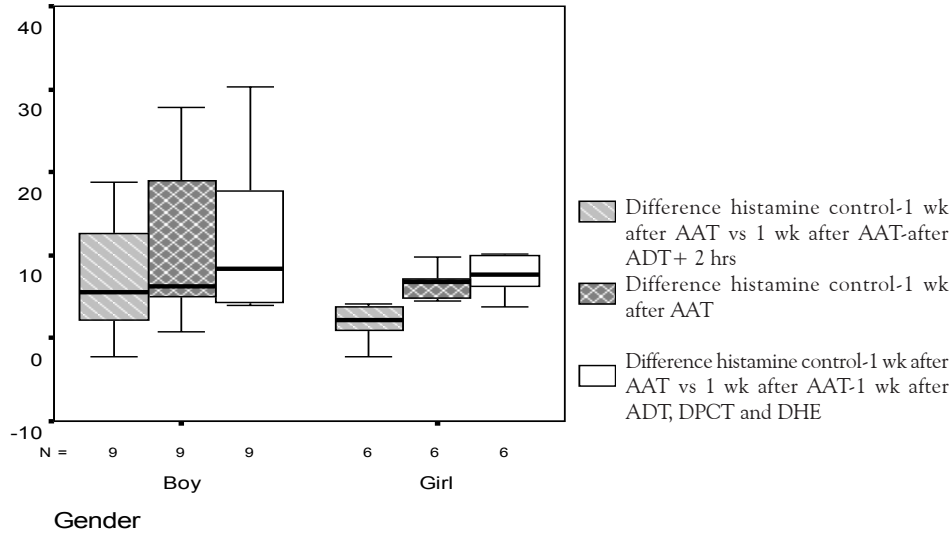

Figure 2. Effectiveness of allergen avoidance therapy (AAT) only *versus* AAT after assisted drainage therapy (ADT) + 5 min, 30 min and 1 week for FEV1

Table 2. Comparison between differences of FEV1 change (%) (Paired t-test)

No	Variables	Mean	SD	P<0.05
1	Control-1 wk AAT vs. 1 wk AAT- 5 min after ADT	-3.867	6.822	0.046
2	Control-1 wk AAT vs. 1 wk AAT-30 min after ADT + DPCT	-5.373	6.680	0.008
3	Control-1 wk AAT vs. 1 wk AAT-1 wk after AAT + ADT, DPCT and DHE	-4.273	5.891	0.014

Notes: Higher negative value indicates that the therapy is more effective (higher difference); AAT= allergen avoidance therapy; ADT=assisted drainage therapy; DPCT = dental plaque control therapy; DHE= dental health education

Table 3. Comparison between serum histamine samples level (ng/ml) (Paired sample t-test, CI= 95%), see also Figure 2.

No	Variables	Mean	SD	P<0.05
1	Control vs. 1 week AAT	0.018	0.322	0.832
2	1 week AAT vs.1 wk AAT + ADT + 2 hrs	1.083	1.020	0.001
3	1 week AAT vs. 1 week after AAT + ADT, DPCT and DHE	1.521	0.995	0.001

Notes: Higher positive value indicates better improvement of serum histamine level; AAT= allergen avoidance therapy; ADT=assisted drainage therapy; DPCT = dental plaque control therapy; DHE= dental health education

Table 4. Comparison between differences of serum histamine level change (ng/ml) (Paired sample t-test, CI 95%)

No	Variables	Mean	SD	P<0.05
1	Control-1 wk AAT vs. 1 wk AAT- 2 hrs after ADT	-0.434	0.741	0.040
2	Control-1 wk AAT vs. 1 wk AAT-1 wk after AA + ADT, DPCT and DHE	-1.503	1.054	0.001

Notes: Higher negative value indicates that the that the therapy is more effective (higher difference); AAT: allergen avoidance therapy; ADT=assisted drainage therapy; DPCT = dental plaque control therapy; DHE= dental health education

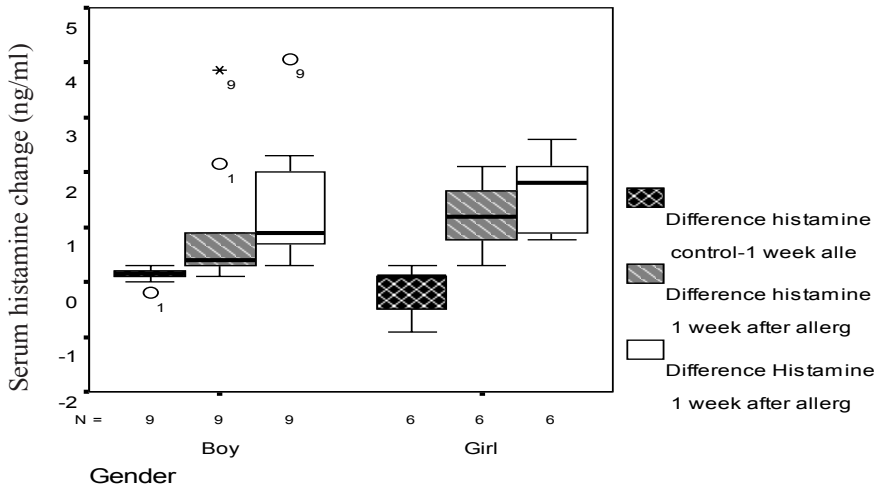

Figure 3. Effectiveness of allergen avoidance therapy (AAT) only versus AAT after assisted drainage therapy (ADT) + 2 hrs and 1week for serum histamine

Discussion

For better understanding of this discussion, a glance of basic medical sciences such as anatomy, physiology; immune and neural system should be reviewed. Additionally, according to literature, there is an interaction between the immunogenic and neurogenic inflammation so called the "neurogenic switching mechanism"[16,21]that should be considered in the asthma etiopathogenesis. Therefore, in our concept, an ideal asthma management protocol should include an integrated management of both inflammations.

The assisted drainage therapy has the propensity for reducing both the trigger of the immunogenic and neurogenic inflammation (by removing subgingival plaque and toxins), and their products (i.e. pro-inflammatory mediators and neuropeptides).[12] These mediators are capable to stimulate the maxillary nerve innervating the oral cavity and propagate antidromically (in reverse direction to the regular neural impulse)[22] via the sphenopalatine ganglion (SPG) which then spread the inflammation to systemic or distant organs.[21,23]

According to Chih Feng and Baraniuk,[24] the neural system has an important role in the sensitivity of respiratory organs, hence the nose. In addition, the SPG, a parasympathetic ganglion has an important role as a relay center between the afferent nerves, the autonomic (the parasympathetic) and sensory nerve (maxillary nerve) which relate to multiple chemical sensitivity (MCS) upon stimulation of allergens, cold, smokes etc.[24] Moreover, further analysis of the interrelationship of the maxillary nerve and asthma is the existence of receptors in the nose and pharynx and, presumably, in the paranasal sinuses that have afferent fibers which became part of maxillary nerve. They pass to the brain stem and connect with the reticular formation of the dorsal vagal nucleus. From the vagal nucleus, parasympathetic efferent fibers travel in the vagus nerve to the bronchi.[25] The interneural relationship between upper and lower respiratory tract is able to explain the "one airway-one disease" concept. Therefore, down-regulation of SPG sensitivity via ADT which led to rapid improvement of respiratory quality (FEV1) is logical.

Rapid improvement of FEV1 after ADT compared to ATT only is shown in Table 1. It could be the effect of rapid reduced expression of pro-inflammatory cytokines (i.e. tumour necrosis factor-α), neuropeptides which involved in the neurogenic switching mechanism (substance P, SP and calcitonin gene-related peptide, CGRP)[16,21] that were "drained out" within the oozed blood caused by ADT. Substance P half life was <6 min and CGRP was 6-10 min after degraded by neuropeptidase.[16] This interesting phenomenon has been verified by Utomo[26] in an animal study, which revealed a sudden fall in SP and CGRP expression 20 min after ADT, with significant difference (P=0.001; CI 95%) compared to control.

Mast cells and basophils are the "traditional" major sources of histamine, whereas current studies

revealed that neutrophils, macrophages, T lymphocytes and dendritic cells which do not store histamine, but are capable of producing and releasing high amounts of histamine.[19] Bacterial dental plaque and their toxins, the proteoglycans, PGN (Gram-positive) and lipopolysaccharides, LPS (Gram-negative), are able to stimulate these immunocompetent cells to produce histamine.[20] However, this stimulation is not limited via the cross-linking mechanism that is only for mast cells and basophils; nevertheless, most immunocompetent cells could be stimulated via the complement receptors (i.e. C3aR for bacteria),[27,28] and toll-like receptors (TLR2 for PGN; TLR2 and TLR4 for LPS).[27]Once formed, histamine is either stored or rapidly inactivated and degraded by enzymes, primarily the diamine oxidase (DAO). The deficiency of this enzyme triggers an allergic reaction because histamine pool in the synapses.[19,29]

Reduced mast cells and basophils stimulations after ADT and DPCT also concomitant with lowered release of mediators i.e. interleukin-3 (IL-3), IL-4, IL-13, histamine and prostaglandins. Decrease of IL-3 leads to reduce either mast cell proliferation or prevention of basophil apoptosis (a IL-3 driven mechanism). Decline of these cells subsequently increases unbounded or free spesific IgE which has very short half life (1-2 days).[30,31] Lowered IL-4 and IL-13 result in the reduction of the isotype switching, thus also the specific IgE serum level.[27] Therefore, it is plausible that the subjects of this study also had lower histamine serum level, improved respiratory quality (FEV1) and gradually free from food allergy.

In this study, allergen avoidance therapy in one week did not show significant difference in serum histamine level. It was logical because the allergen avoidance therapy was meant for the inhibition of specific IgE receptors (FcεRI) cross-linking by their free specific IgE from food allergens that occurred in mast cells and basophils. Cross-linking led to activation or degranulation that produced histamine. Unfortunately, the previous attached specific IgE either to mast cells or basophils had a half life of 10 – 20 days.[30,31] Therefore, actual significant difference could be achieved after about 2-3 weeks later. Albeit our study did not examine specific IgE serum level; the successful reduction of allergic reaction also proved by the low serum histamine level samples that nearly zero (0.014 ± 0.037ng/ml) one week after ADT, DPCT and DHE. It was suggested resulted from decreased cross-linking by IgE.

Our study was contradictory to Arbes et al[9] who showed that lower allergy prevalence existed in people with higher serum IgG to *Porphyromonas gingivalis*, and Friedrich et al[10] who revealed that periodontitis patients were allergy-resistant; these studies were in accordance with the hygiene hypothesis. However, this contradiction could be explained by understanding our concept. Following ADT, DPCT and self oral hygiene maintenance, oral pathogenic bacteria, toxins and pro-inflammatory mediators diminished which led to decrease the neurogenic switching mechanism and stimulation of immunocompetent cells which are responsible in allergic asthma reaction.

We conclude that remarks, the assisted drainage therapy is effective for rapid improvement of respiratory quality and reducing allergic symptoms in mild persistent asthmatic children. Therefore, it could be proposed as an adjuvant in children's allergic asthma management.

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