09. The role of house dust mite immunotherapy in Indonesian

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Research article

The role of house dust mite immunotherapy in Indonesian children with chronic rhinosinusitis allergy: A randomized control trial

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ABSTRACT

Background: Chronic rhinosinusitis allergy (CRA) is a disease that is commonly found in children and is mostly caused by allergy to house dust mites (HDM). The use of HDM immunotherapy can be considered in children with allergies.
Objectives: Analyzing the impact of mite immunotherapy on disease burden in Indonesian children with CRA.
Methods: A randomized control trial study was conducted to participants in 2 groups, namely the immunotherapy group (n = 25) and the non-immunotherapy group (n = 25). Participants were given HDM immunotherapy for 14 weeks, which was given once per week. Participants during therapy were evaluated for rhinosinusitis symptoms and measured their immunity status (specific IgE), sleep quality (SDSC), quality of life (SN5), and family coping (F-COPES) pre-post therapy. Statistical analysis used in this study included paired t-test, Wilcoxon test, independent t-test, or Mann Whitney test with $p < 0.05$.
Results: The value of specific IgE in the immunotherapy group was 4.12 ± 7.75 kU/l (pre-test) and 1.52 ± 2.42 kU/l (post-test; $p < 0.001$), while in the non-immunotherapy group was 1.47 ± 3.28 kU/l (pre-test) and 1.18 ± 2.81 kU/l (post-test; $p = 0.317$). The SDSC value in the immunotherapy group was 42.16 ± 2.75 (pre-test) and 30.32 ± 3.22 (post-test; $p < 0.001$), while in the non-immunotherapy group was 41.92 ± 2.75 (pre-test) and 41.84 ± 2.87 (post-test; $p = 0.987$). The F-COPES value in the immunotherapy group was 101.56 ± 5.78 (pre-test) and 105.20 ± 4.31 (post-test; $p = 0.015$), while in the non-immunotherapy group was 100.36 ± 9.63 (pre-test) and 99.96 ± 9.98 (post-test; p = 0.224). The SN-5 value in the immunotherapy group was 30.04 ± 2.78 (pre-test) and 11.00 ± 2.33 (post-test; $p < 0.001$), while in the non-immunotherapy group was 30.04 ± 2.78 (pre-test) and 30.04 ± 2.78 (post-test; $p = 0.767$). There was a significant comparison between the immunotherapy group and the non-immunotherapy group on the specific IgE ($p = 0.013$), SDSC ($p < 0.001$), and SN-5 ($p < 0.001$) values. Meanwhile, there was no significant difference in the F-COPES value ($p = 0.129$).
Conclusions: The administration of HDM immunotherapy can improve the participant's immunity, quality of life, and sleep disorder.

1. Introduction

Chronic rhinosinusitis is an inflammation of the mucosa of the paranasal sinuses and nose [1, 2], which is commonly found in children [3, 4]. Rhinosinusitis affects approximately 5–15% of the population, of which 2–4% is chronic rhinosinusitis [5]. As much as 69.8% of chronic rhinosinusitis cases were identified positive due to house dust mites (HDM) allergy, of which 42.5% occurred in children [6]. A recent Indonesian study found that the causes of allergy in children included HDM (63.16%), cockroach (42.85%), fungi/mold spore (42.85%), grass pollen (23.4%), and crab (21.9%) [7]. Chronic rhinosinusitis allergy (CRA) in children greatly disrupts physical activity of both patient and parents or caregiver. This condition affects the adaptability of the family, quality of life, and finances [3, 5, 8]. The costs needed include healthcare and hospitalization, drugs costs, transportation, cost of medical insurance and seeking healthcare information, in which allergy patients tend to experience recurrence so that additional costs often arise [9].

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CRA caused by HDM has yet to be treated using pharmacotherapy [10], hence it still cannot reduce the prevalence of respiratory allergies such as chronic rhinosinusitis [5, 11]. Therefore, alternative therapy is needed to manage the problem. Current development of alternative allergy management is immunotherapy [10, 12]. Immunotherapy is a treatment that has been shown to reduce allergy symptoms in the long term [11, 13]. In addition, immunotherapy may decrease the inflammatory response [6, 14] and improve the quality of life of children with CRA [15].

Some literatures stated that HDM immunotherapy is a solution for chronic rhinosinusitis. However, the provision of HDM immunotherapy in patients with chronic rhinosinusitis is still limited and the success rate is still uncertain. The number of cases of HDM allergy in children in Dr. Soetomo General Academic Hospital had increased annually in 2017 (115 cases) and 2018 (142 cases). Based on the description above, it is necessary to analyze the effect of HDM immunotherapy on specific IgE, sleep disturbances, quality of life, and coping in children with chronic rhinosinusitis.

2. Methods and materials

2.1. Participants

Participants in this study were children diagnosed with rhinosinusitis. Participant's inclusion criteria included children aged 3–18 years [16, 17], diagnosed with chronic rhinosinusitis according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) [18, 19], and reactive skin prick test results using HDM allergen. The exclusion criteria for the participants included abnormal shapes in the anatomy of the nose and paranasal sinuses, patients diagnosed with cancer, having an autoimmune disease, being diagnosed with cerebral palsy, and Down syndrome. Legal parents or guardians first received an explanation regarding the research objectives prior to the study. They had to fill in and give a signature on the consent form should they agreed to become participants.

2.2. Study design

A randomized control trial was conducted in immunotherapy group and non-immunotherapy group, with each group consisting of 25 participants (Figure 1). The immunotherapy group received rhinosinusitis therapy plus HDM immunotherapy, while the non-immunotherapy group only received rhinosinusitis therapy. The given rhinosinusitis therapy included antihistamines, intranasal steroids, systemic steroids, and antibiotics should complications found [6]. The research was conducted in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January to December 2019. HDM immunotherapy was provided for 14 weeks, with immunotherapy being given once a week. The participant's specific-IgE serum, sleep quality, family coping, and quality of life were measured before and after administrating immunotherapy. During the immunotherapy, the participant's clinical condition was monitored based on the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) [19] every week.

2.3. Ethical approval

This study has been registered in the Thai Clinical Trial Registry/TCTR (TCTR20191001002) and has received ethical approval at the Health Research Ethics Committee Dr. Soetomo General Academic Hospital Surabaya, Indonesia (1325/KEPK/VII/2019). Participants and caregivers received explanations related to research prior to the implementation of the intervention. The caregiver filled out the consent form without coercion.

2.4. House dust mite immunotherapy

House dust mite immunotherapy (Teaching Industry Allergen by Dr. Soetomo Hospital-Universitas Airlangga, Surabaya, Indonesia) used was an extract of *Dermatophagoides pteronyssinus* with 11.3–26.6 ng/mL via subcutaneous injections [12, 20]. The dose of immunotherapy used every week varied: 0.1 cc (first week), 0.15 cc (second week), 0.22 cc (third week), 0.32 cc (fourth week), 0.48 cc (fifth week), 0.72 cc (sixth week), 1 cc (seventh week), 0.1 cc (eighth week), 0.15 cc (ninth week), 0.22 cc (tenth week), 0.32 cc (eleventh week), 0.48 cc (twelfth week), 0.72 cc (thirteenth week), and 1 cc (fourteenth week) [12]. The use of HDM immunotherapy was based on a previous study in Indonesia, stating that the most types of HDM found were *Dermatophagoides pteronyssinus* (87%), *Dermatophagoides farinae* (7%), and *Bromia tropicalis* (6%) [21]. Another study also stated that the most HDM found in Indonesia was *Dermatophagoides pteronyssinus* that could be found in various places such as beds, floors, and sofas, while *Dermatophagoides farinae* was mostly found on sofas. *Bromia tropicalis* was the least compared to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* [22].

2.5. Rhinosinusitis symptoms

Symptoms of chronic rhinosinusitis were monitored based on the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) [19]. Signs and symptoms of chronic rhinosinusitis include itchy nose, nasal congestion, cough, snoring, sneezing, nasal drip, runny nose, swallowing pain, wheezing, shortness of breath, ear discharge, watery eyes, and red eyes. The rhinosinusitis symptoms were evaluated using an observation sheet when the child was given HDM immunotherapy in accordance with the dose. The evaluation was conducted until the rhinosinusitis symptoms disappear. The unit of measurement for this symptom was weeks [20].

2.6. Measurement of serum specific IgE levels

Participants were taken +3 ml of venous blood and stored in an EDTA tube. Measurement of serum specific IgE levels used an enzyme-linked immunosorbent assay/ELISA (Euroline ™; Euroimmun AG, Lübeck, Germany). Indirect ELISA examination was conducted by taking the patient's blood serum from the vein as much as 6 mL, and was then rotated at 3000 rpm for 15 min. The serum was stored at -20 °C to keep the condition stable. Specific ring allergens for certain allergens were inserted in the wells and then incubated with the patient's sample. Should the patient's sample was positive, the specific IgE in the patient's serum would bind to the allergen. This antibody-gen binding could be detected by adding a monoclonal anti-human IgE conjugate. The length of time to check serum IgE levels was 3.5 h. The serum IgE determination was in the range of 0.35–100 kU/l.

2.7. Measurement of sleep disturbance scale for children

Participant's sleep disturbance was assessed using the Sleep Disturbance Scale for Children (SDSC). The SDSC assesses sleep disturbances based on the intensity or frequency of each of the following categories: score 1 for never, score 2 for infrequent (≤1–2 times/month), score 3 for occasional (1–2 times/week), 4 for often (3–5 times/week), and 5 for always (every day). The cut-off point of the total score was 39, then sleep disturbance was diagnosed should the total score was more than 39 [23, 24]. The Indonesian version of SDSC was declared valid and reliable [24] with $\alpha = 0.81$ [25].

2.8. Measurement of family crisis oriented personal evaluation scale

Family crisis oriented personal evaluation scales (F-COPES) are tools used to assess family coping consisting of 30-item questions. The F-COPES consists of 5 sub-scales (obtaining social support, seeking spiritual support, reframing, mobilizing family support, and passive assessments) which were assessed using Likert's scale [26, 27]. The Indonesian version of F-COPES was declared valid and reliable with a value of $\alpha = 0.89$ [27, 28].

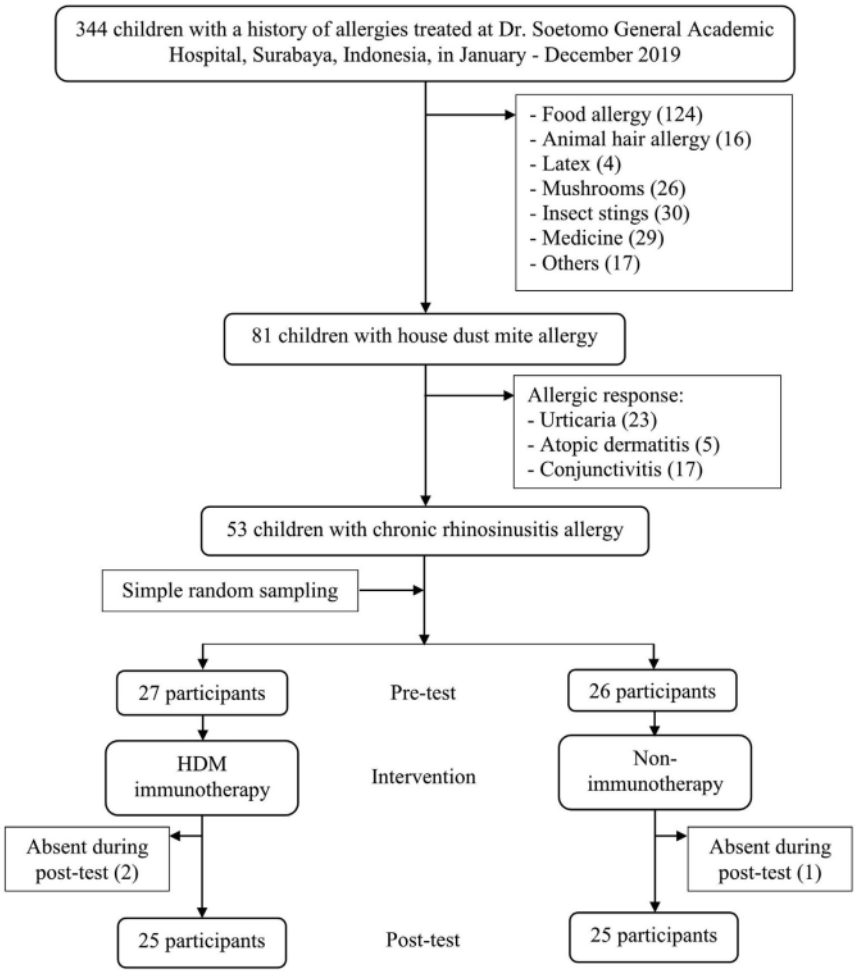

Figure 1. Screening process in participant recruitment.

2.9. Measurement of Sino-Nasal Quality of Life

Sino-Nasal Quality of Life (SN-5) is a questionnaire used to measure the patient's health status and quality of life for rhinosinusitis. The SN-5 consists of 6 question items, of which 5 question items have a score of 1–7 (None of the time = 1; Hardly any time at all = 2; A small part of the time = 3; Some of the time = 4; A good part of the time = 5; Most of the time = 6; All of the time = 7) and 1 question item is a visual analog scale (VAS). The higher the score, the worse the health status and quality of life of children with chronic rhinosinusitis [29]. The Indonesian version of SN-5 was a valid and reliable tool, with the value of $\alpha = 0.76$ [30,31].

2.10. Statistical analysis

The data were first tested using Kolmogorov-Smirnov. Furthermore, data on participant's characteristics were analyzed using independent t-test or the Mann-Whitney test. In addition, other measurement results were analyzed using independent t-test or Mann-Whitney test and dependent t-test or Wilcoxon test. The statistical test results were declared significant if $p < 0.05$. Data analysis used IBM SPSS Statistics software version 23.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Characteristics of participant

The average age of group I participants was 100.44 ± 46.81 months and group II was 88.60 ± 41.79 months ($p = 0.362$). Most participants were boys (56%), consisting of 64% in group I and 48% in group II ($p = 0.388$). Most participants had a history of cesarean delivery (64%), both in group I and group II ($p = 1{,}000$). Most participants had a history of not consuming exclusive breastfeeding (64%), consisting of 60% in group I and 68% in group II ($p = 0.727$; Table 1).

3.2. Immunotherapy group

The measurement results in the immunotherapy group showed that the pre-test and post-test IgE value was 4.12 ± 7.75 kU/l and 1.52 ± 2.42 kU/l, respectively ($p < 0.001$). The pre-test and post-test SDSC value was 42.16 ± 2.75 and 30.32 ± 3.22, respectively ($p < 0.001$). The pre-test and post-test SN-5 value was 30.04 ± 2.78 and 11.00 ± 2.33, respectively ($p < 0.001$). Meanwhile, the pre-test and post-test F-COPES value was 101.56 ± 5.78 and 105.20 ± 4.31, respectively ($p = 0.015$; Table 2).

Table 1. Participant characteristics.

Characteristics	Immunotherapy (n = 25)	Non-immunotherapy (n = 25)	*p*
Sex (%)			
Male	16 (64.0)	12 (48.0)	0.388
Female	9 (36.0)	13 (52.0)	
Labor history (%)			
Spontaneous	9 (36.0)	9 (36.0)	1.000
C-section	16 (64.0)	16 (64.0)	
Exclusive breastfeeding (%)			
Yes	10 (40.0)	8 (32.0)	0.727
No	15 (60.0)	17 (68.0)	
Atopic history (%)			
Yes	17 (68.0)	16 (64.0)	1.000
No	8 (32.0)	9 (36.0)	
Family history of atopy (%)			
Yes	17 (68.0)	16 (64.0)	1.000
No	8 (32.0)	9 (36.0)	

3.3. Non-immunotherapy group

There was no significant difference between pre-test and post-test in the participants of the non-immunotherapy group. The average pre-test and post-test IgE value was 1.47 ± 3.28 kU/l and 1.18 ± 2.81 kU/l, respectively ($p = 0.317$). The pre-test and post-test SDSC score was 41.92 ± 2.75 and 41.84 ± 2.87, respectively ($p = 0.987$). The pre-test and post-test SN-5 value was 30.04 ± 2.78 and 30.04 ± 2.78, respectively ($p = 0.767$). Meanwhile, the pre-test and post-test F-COPES value was 100.36 ± 9.63 and 99.96 ± 9.98, respectively ($p = 0.224$; Table 2).

3.4. Comparison of immunotherapy and non-immunotherapy groups during pre-test and post-test therapy

In the immunotherapy group, the difference of specific IgE value between pre-test and post-test was 3.98 ± 7.42 kU/l, while the difference of specific IgE value between pre-test and post-test in the non-immunotherapy group was 0.29 ± 2.02 kU/l ($p = 0.013$). On the other hand, the difference of SDSC score between pre-test and post-test in the immunotherapy group (11.84 ± 4.83) was higher than the non-immunotherapy group (0.08 ± 0.40; $p < 0.001$). Significant difference was also found in the SN-5 value, in which the immunotherapy group (19.04 ± 3.65) was higher than the non-immunotherapy group (0.04 ± 3.80; $p < 0.001$). Meanwhile, there was no significant difference of F-COPES value between the immunotherapy group (3.24 ± 3.65) and the non-immunotherapy group (-0.80 ± 13.30; $p = 0.129$; Table 3).

On the pre-test, there was no significant comparison between the treatment and control groups on SDSC ($p = 0.731$), SN5 ($p = 1.000$), F-COPES ($p = 0.961$), and IgE ($p = 0.087$). After the administration of immunotherapy, there was no significant comparison between the treatment group and the control group on F-COPES ($p = 0.119$) and IgE ($p = 0.496$) measurements. Meanwhile, there was a significant comparison of SDSC value ($p < 0.001$) and SN5 ($p < 0.001$) between the treatment group and the control group after giving immunotherapy.

The evaluation of 14-weeks HDM immunotherapy showed a significant difference between the immunotherapy group and the non-immunotherapy group. Itchy nose symptom disappeared at 6.4 ± 2.64 weeks and 15.0 ± 0.00 weeks in immunotherapy and non-immunotherapy group, respectively ($p < 0.001$). Stuffy nose symptom in the immunotherapy group (8.0 ± 1.58 weeks) improved earlier than the non-immunotherapy group (15.0 ± 0.00 weeks; $p < 0.001$). The cough experienced by subjects in the non-immunotherapy group (8.0 ± 1.28 weeks) was longer than that experienced in the immunotherapy group (15.0 ± 0.00 weeks; $p < 0.001$). The snoring symptom in the immunotherapy group (8.0 ± 1.28 weeks) improved earlier than the non-immunotherapy group (10.8 ± 6.87 weeks; $p < 0.001$). In the immunotherapy group, sneezing symptom (5.8 ± 2.73 weeks) improved earlier than in the non-immunotherapy group (15.0 ± 0.00 weeks; $p < 0.001$). In the immunotherapy group, the use of nasal drip was shorter (7.4 ± 1.58 weeks) than in the non-immunotherapy group (15.0 ± 0.00 weeks; $p < 0.001$). Colds experienced by the non-immunotherapy group (15.0 ± 0.00 weeks) were more prolonged than the immunotherapy group (8.0 ± 1.58 weeks; $p < 0.001$). Swallowing pain in the immunotherapy group

Table 2. Comparison of research variables before and after the administration of immunotherapy in each group.

Variable	HDM Immunotherapy		*p*
	Pre-test	Post-test	
Immunotherapy Group			
Specific IgE	4.12 ± 7.75	1.52 ± 2.42	<0.001**
SDSC	42.16 ± 2.75	30.32 ± 3.22	<0.001**
SN-5	30.04 ± 2.78	11.00 ± 2.33	<0.001**
F-COPES	101.56 ± 5.78	105.20 ± 4.31	<0.015*
Non-Immunotherapy Group			
Specific IgE	1.47 ± 3.28	1.18 ± 2.81	0.317
SDSC	41.92 ± 2.75	41.84 ± 2.87	0.987
SN-5	30.04 ± 2.78	30.04 ± 2.78	0.767
F-COPES	100.36 ± 9.63	99.96 ± 9.98	0.244

Abbreviations: HDM = house dust mite; SDSC = sleep disturbance scale for children; SN-5 = sino-nasal 5 quality of life; F-COPES = Family crisis oriented personal evaluation scales; *significant $p < 0.05$; **significant $p < 0.001$.

Table 3. Comparison of the difference in measurement values between immunotherapy group and non-immunotherapy group.

Variable	Group		p
	Immunotherapy	Non-immunotherapy	
Specific IgE	3.98 ± 7.42	0.29 ± 2.02	0.013*
SDSC	11.84 ± 4.83	0.08 ± 0.40	<0.001**
SN-5	19.04 ± 3.65	0.04 ± 3.80	<0.001**
F-COPES	3.24 ± 3.65	-0.80 ± 13.30	0.129

Abbreviations: SDSC = Sleep Disturbance Scale for Children; SN-5 = Sino-Nasal 5 Quality of Life; F-COPES = Family crisis oriented personal evaluation scales; *significant $p < 0.05$; **significant $p < 0.001$.

disappeared at 0.6 ± 1.28 weeks, but the symptoms disappeared at 9.5 ± 6.76 weeks in the non-immunotherapy ($p < 0.001$). In the immunotherapy group, wheezing symptom improved earlier (3.9 ± 4.19 weeks) than the non-immunotherapy group (10.8 ± 6.87 weeks; $p < 0.001$). The shortness of breath experienced by participants in the non-immunotherapy group (10.8 ± 6.87 weeks) disappeared longer than the immunotherapy group (4.0 ± 4.33 weeks; $p < 0.001$). A significant difference between the non-immunotherapy group (1.2 ± 1.73 weeks) and the immunotherapy group (12.0 ± 6.12 weeks) was also found in ear discharge symptom ($p < 0.001$). There was no significant difference in watery eyes symptom in the immunotherapy group (3.2 ± 3.58 weeks) and the non-immunotherapy group (7.2 ± 7.64 weeks; $p = 0.171$). Similar condition was found in red eye symptom, where the non-immunotherapy group disappeared at 4.8 ± 7.14 weeks and the immunotherapy group disappeared at 1.8 ± 2.38 weeks ($p = 0.965$; Figure 2).

4. Discussion

Based on several studies, the use of specific allergy immunotherapy is believed to reduce pharmacotherapy, in which the focus of the immunotherapy system is to alter the Th2 bias immune response, whereas pharmacotherapy only acts on symptoms [10, 32, 33]. Specific-allergy immunotherapy causes changes in immune system modulation from Th2 to Th1 [34,35]. Immunotherapy increases levels of regulatory T cells which have a direct effect on B cells by reducing the frequency of IgE-secreting plasma cells and simultaneously increasing the frequency of IgG4-secreting plasma cells [35, 36] that result in a gradual decrease in serum allergen-specific IgE levels [34, 35]. This study on the use of immunotherapy specific allergy (HDM) plus pharmacotherapy is in accordance with previous studies. This study involved a pre-test and post-test evaluation on serum-specific IgE levels, sleep disturbances, quality of life, and caregiver coping. Moreover, this study evaluated the arisen symptoms during the implementation of immunotherapy [36, 37].

The value of IgE-specific allergy in the immunotherapy group decreased significantly compared to the non-immunotherapy group. A previous study found a change in the immunological response after giving immunotherapy, in which IgG4 increased from week 1–8 which then stabilized. As IgG4 is a competitive inhibitor of specific IgE, therefore when IgG4 increases, specific IgE decreases [38]. This condition is consistent with several previous studies that found a significant difference in decreasing IgE-specific allergy levels in the immunotherapy group and non-immunotherapy group, where the decrease in IgE was more significant in the immunotherapy group [39]. Similar condition was also found in adult patients, in which a decrease in IgE-specific

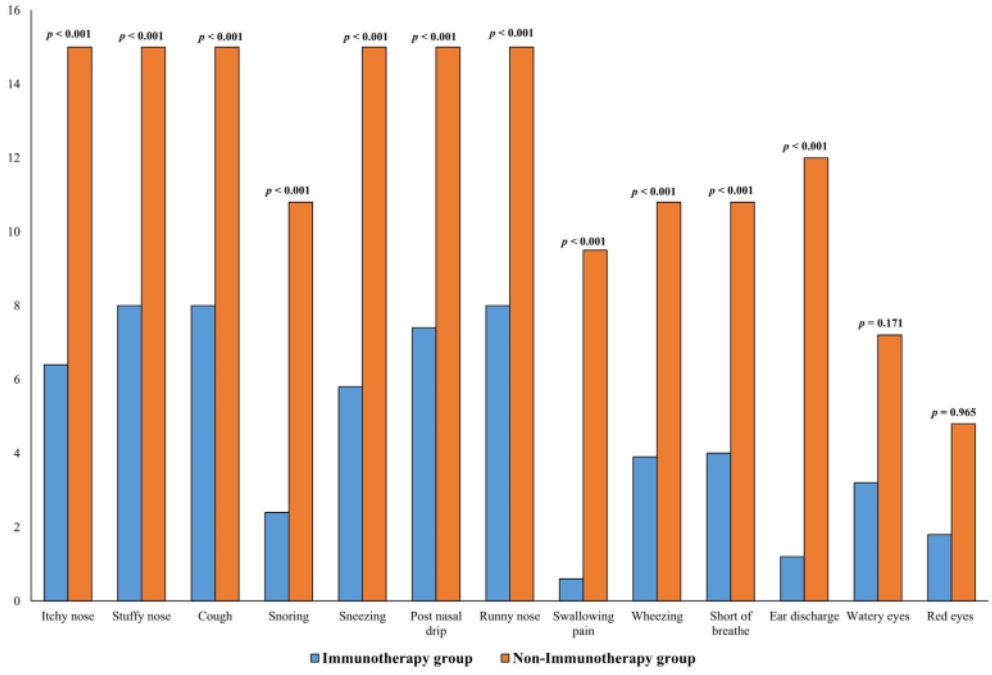

Figure 2. Comparison of immunotherapy group and non-immunotherapy group during rhinosinusitis therapy symptom disappeared.

allergy value was more significant in the immunotherapy group [40]. A recent study also found the value of IgE-specific allergy against *D. pteronyssinus, D. farinae, D pter 1* and *D pter 2* had a significant decrease in the immunotherapy group [41].

This study found a significant difference in the value of participant's sleep disorders between the immunotherapy group and the non-immunotherapy group, in which the participants in immunotherapy group experienced improved sleep after receiving HDM immunotherapy. Previous studies stated that 54% of pediatric and adult patients experienced improvements in sleep disorders after HDM immunotherapy [42]. Similar condition was also found in children who experienced HDM allergy where they experienced improved sleep, especially in the immunotherapy group [43]. In another study, it was found that participant's sleep improved after receiving HDM immunotherapy with various allergy responses, including rhinitis [44], asthma [45], atopic dermatitis atopic, bronchial hyper-responsiveness [46], and conjunctivitis [47].

Participants in the immunotherapy group experienced better quality of life than the non-immunotherapy group. Based on several previous studies, it was found that the use of specific allergy immunotherapy can improve the participant's quality of life due to improved allergy symptoms [42]. Another study also stated that the administration of immunotherapy to allergic patients significantly improved their quality of life [48]. Recent studies also found that giving participants specific immunotherapy can improve their quality of life, which is followed by a decrease in the intensity of allergy recurrence found after the use of immunotherapy [49]. Immunotherapy has been shown to improve the quality of life of participants by reducing the intensity of allergy symptoms, improving physical condition, and also reducing dependence on drug consumption [10, 42, 48, 49].

There was no significant difference in family coping between the immunotherapy group and non-immunotherapy group. However, this study found a significant difference in the immunotherapy group at the pre-test and post-test. Family coping is an important component in the success of therapy in children, including those with CRA. In general, the support that participants get is from their families, both instrumental and informative support [50]. Coping strategy that is often found in participant's families is that they decide to stop CRA therapy because of financial problems and recurring symptoms [51]. The problems faced can be solved with a combination of coping strategies, namely problem-focused coping and emotion-focused coping [52].

This study evaluated the symptoms of CRA during the 14-week HDM immunotherapy, which found a significant difference between the immunotherapy group and the non-immunotherapy group. Previous studies have suggested that the use of specific immunotherapy can improve the symptoms of CRA, namely sneezing, runny nose and stuffy nose [53]. Other studies have also stated that the improvement in symptoms of CRA can be significantly improved with the use of specific immunotherapy [42]. The use of specific allergy immunotherapy has been shown to shorten the symptoms of CRA, which is usually 14 weeks, can be reduced to 3–4 weeks [49].

This research, however, is subject to several limitations. First, due to limited research period caused by the Covid-19 pandemic, this study could only evaluate the therapy in the build-up phase. Second, the number of participants is insufficient in each category, therefore it is necessary to add the ideal proportion to minimize bias in further research.

5. Conclusion

Chronic rhinosinusitis caused by HDM allergy is a health problem that is often found in children. The incidence has increased every year in Indonesia. The use of HDM immunotherapy for 14 weeks is proven to be able to improve the health status of children with CRA cause by HDM. Improvements in health status include improvement in clinical symptoms of chronic rhinosinusitis, decreased serum-specific IgE, decreased sleep disturbances, and improved quality of life for children with CRA caused by HDM.

Declarations

Author contribution statement

Azwin Mengindra Putera: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Zahrah Hikmah, Anang Endaryanto: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Irwanto, Margarita Maria Maramis: Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

The clinical trial described in this paper was registered at Thai Clinical Trials Registry under the registration number TCTR20191001002.

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