

Standardized Sublingual Immunotherapy for Mites in Pediatric Patients, in a Six-Year Follow-Up Period, in a High Specialty Hospital in the City of Mexico

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Abstract

Introduction: Specific immunotherapy with allergens is the only treatment that can modify the natural course of allergic diseases. The dust mite is one of the most common aeroallergens in allergic rhinitis, allergic asthma and atopic dermatitis.

Justification: It is a therapy that is commonly administered to children because of its ease of application, and the adverse effects are less than with subcutaneous immunotherapy.

Objective: Describe the characteristics of patients aged 4 - 16 years who receive standardized sublingual immunotherapy against mites,

Method: Cross-sectional, observational, descriptive and retrospective study that includes patients diagnosed with allergic rhinitis, asthma and/or atopic dermatitis with positive skin tests exclusively for mites undergoing treatment with standardized sublingual immunotherapy for at least two years.

Statistical Analysis: With the study variables, the statistical program SPSS version 21 will be analyzed, with which the analysis will be carried out according to the type of variable and the results will be presented in tables and graph.

Results: The results of the case analysis are shown. of 63 patients, of these, it was found that 22 corresponded to female patients (34.9%). 100% of the patients had the diagnosis of allergic rhinitis; 74.5% also presented asthma and 6.3% of them also presented atopic dermatitis. No relationship was found between the size of the largest diameter of the papule measured in positive skin tests for mites. The average age of onset of sublingual immunotherapy to mites was 9.24 years, with an average treatment duration of 33.5 months. Immunotherapy effectiveness was reported in 88.9% of patients, 57.1% presented at some time assistance in the emergency department. 9.5% had adverse effects, the most common was local reaction in 7.9% and in 1.6% urticarial reaction.

Discussion: The prevalence of allergic diseases has increased considerably in the last 30 - 40 years. In our study, all cases presented allergic rhinitis; 74.5% also presented asthma and 6.3% of them also presented atopic dermatitis, 19% of the patients presented all three diseases. No relationship was found between the severity of allergic rhinitis with the size of the larger diameter of the papule versus each mite measured in skin tests.

Conclusion: Sublingual immunotherapy against mites is a specific treatment capable of controlling diseases such as allergic rhinitis, asthma and atopic dermatitis, as we find that it efficiently reduces both the symptoms, and the need for subjective pharmacological treatment, and that it is safe its administration.

Keywords: Sublingual Immunotherapy; Rhinitis; Atopic Dermatitis; Asthma

Introduction

Allergen-specific immunotherapy (ITA) is the specific treatment capable of controlling certain allergic diseases. It is the only treatment that can modify the natural course of allergic diseases and is considered, today, an effective treatment, with a level of class A evidence, capable of efficiently reducing both the symptoms and the need for treatment Pharmacological in patients with allergic diseases [1].

Immunotherapy consists of the administration, subcutaneously or sublingually, of the allergen identified as the cause of the disease, in order to ensure that, after subsequent natural contact with the allergen, the clinical symptoms that the patient had did not occur and, therefore, exposure tolerance is achieved by modifying the immune response (immunomodulation) [2].

There is already extensive experience in the sublingual pathway and its effectiveness at the local and systemic level is well documented. The sublingual route is an excellent alternative to the subcutaneous route in children [2].

Specific immunotherapy with allergens has been recognized by the World Health Organization as the only treatment for the cause of diseases such as allergic rhinitis and asthma. In addition, it is an effective treatment for atopic dermatitis [3,4].

One of the most frequent causes of respiratory allergies is the fecal particles excreted by mites, which can be suspended in the air and reach the airway [5].

Mites are microscopic arthropods that cohabit with man in the domestic environment, mainly in the dust accumulated in beds, mattresses, clothes, furniture and carpets.

Epidemiologically it has been reported, the prevalence of allergic diseases that have increased considerably in the last 30 - 40 years and in the industrialized world it is estimated that about 25% of all children have some form of allergic problem. Specifically, atopic dermatitis, allergic rhinitis and bronchial asthma, are diseases that typically develop in childhood and may not be considered as minimal disorders, but as chronic diseases that cause unpleasant symptoms and that affect the quality of life of patients and their families [6,7].

However, asthma is the most prevalent chronic respiratory disease in the world, affecting more than 300 million people of all ethnic groups and ages [8-10].

The International Study of Asthma and Allergies in Children (ISAAC) reported worldwide atopic dermatitis rates, from 2 to 16% in children between 6 and 7 years old, and from 1 to 17% in those between 13 and 14 years old of age. 7 as well as the prevalence of asthma increased globally in children and adolescents from 11.1 to 11.6% and from 13.2 to 13.7%, respectively [8-10].

In Mexico, according to the WHO, 7% of the population suffers from asthma, which means approximately 8.5 million Mexicans sick from this chronic respiratory condition. The General Directorate of Health Information (DGIS) noted that in 2013, 126,952 hospital discharges were registered for all respiratory diseases, of which 25,630 correspond to asthma (20% of respiratory diseases). The population of 0 - 14 years is the most affected [9-13].

In Mexico, studies on the prevalence of allergic rhinitis carried out using the ISAAC methodology have shown wide variations in their results; in Ciudad Victoria, Mexicali, Monterrey and Tijuana a prevalence of 24% was found over the presence of symptoms of rhinitis in the last 12 months and in Mexico City between 29.5 and 47.7% were reported in the population aged 6 to 14 years [10,15].

It has been reported that immunotherapy with dust mite is one of the most common sources of aeroallergens in indoor environments and is cosmopolitan. Due to perennial exposure, sensitization to these can begin at an early age and develop in the life of the individual in multiple diseases such as allergic rhinitis, allergic asthma and atopic dermatitis, among others [11].

It is estimated that 1 - 2% of the world's population is allergic to dust mites. The *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* species are involved in 90% of dust mite allergies. In Latin America and the United States, however, the prevalence of sensitization to *Dermatophagoides pteronyssinus* is 37% and *Dermatophagoides farinae* is 34% [12,15-19].

The immune response to dust mites occurs when aeroallergens penetrate the epithelium of the airway, which in subjects predisposed to allergy, stimulate the migration of dendritic cells to the lymph nodes. Inflammation in the airway is directed by dendritic cells and is stimulated by immunity mediated by Th2.12 cells [12,20-23].

Published studies report the efficacy and safety of sublingual immunotherapy (ITSL) with house mites in allergic rhinitis and allergic asthma using *Dermatophagoides farinae* with reduced symptoms and medication consumption [12,13].

On the other hand physiopathologically; Specific allergen immunotherapy triggers multiple mechanisms sequentially that work together and that lead to clinical events that promote rapid desensitization, allergen-specific immune tolerance and suppression of the allergic inflammatory response [11,19-26].

Sublingual immunotherapy takes advantage of the tolerogenic environment of the oral mucosa to promote allergen tolerance, in which the dendritic cells that are exposed to the allergen promote the change of the pro-allergenic response of T helper 2 (Th2) cells to an inflammatory response T helper 1 (Th1) and the production of interleukin 10 (IL-10) and tumor growth factor B (TGF-B) by regulatory T cells and tolerogenic dendritic cells suppress the responses of specific allergen T cells. Sublingual immunotherapy (ITSL) also promotes the synthesis of specific immunoglobulin G (IgG) and allergen IgA antibodies that block the formation of IgE-allergen complexes and binding to inflammatory cells, promoting an anti-inflammatory environment [11,12]. Specific allergen immunotherapy (ITA) results in a decrease in histamine releasing factors by mononuclear cells, also with a decrease in the proliferation of specific CD4 + allergen cells and alterations in cytosine T cells with a decrease in their recruitment to allergen challenge sites, such as skin or sublingual area [11,27-30].

Methodology

Study design

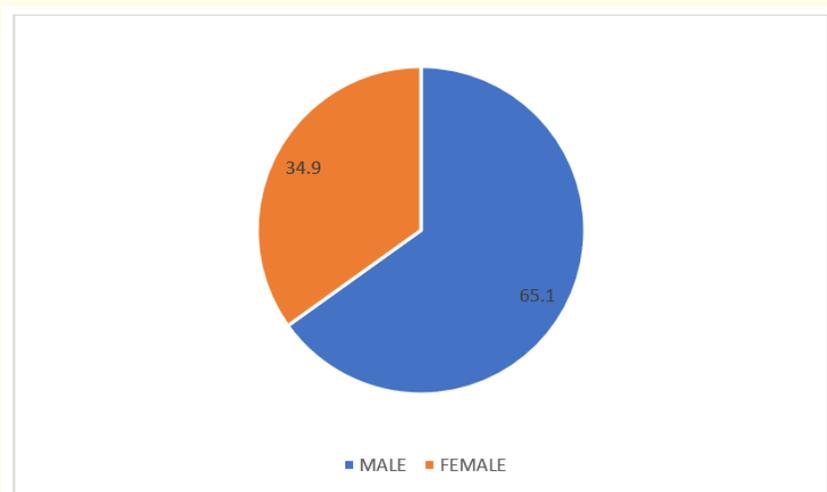
This is a study: cross-sectional, observational, descriptive and retrospective, consisting of a cohort of patients diagnosed with allergic rhinitis, atopic dermatitis or asthma with positive skin tests exclusively for mites (*Dermatophagoides farinae* and/or *Dermatophagoides pteronyssinus*) who received sublingual immunotherapy for at least two years during the period from April 2013 to March 2019 at the National Institute of Pediatrics, in Mexico City, excluding the files of patients who were reactive to other allergens in addition to or other than mites in skin tests and have less than two years with the treatment.

With the study variables, the information was analyzed in a statistical program SPSS version 21, the information obtained was described in tables and graphs.

The objective of the study was to describe the characteristics of 4-16 patients receiving standardized sublingual immunotherapy against mites ((*Dermatophagoides farinae* and/or *Dermatophagoides pteronyssinus*) for the treatment of conditions such as allergic rhinitis, asthma and atopic dermatitis, during the period studied.

Results

We found a total of 120 records of which 63 (52.5%) were included for the analysis. Of these, it was found that 22 (34.9%) corresponded to female patients (See graph 1).



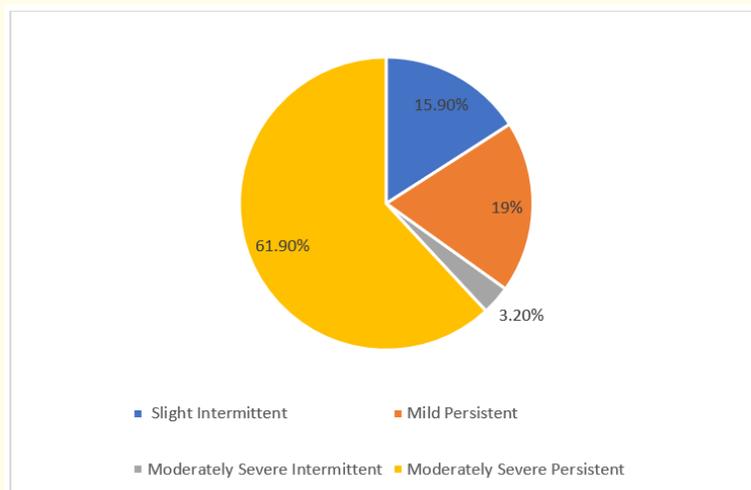
Graph 1: Distribution of cases regarding sex in patients with mite allergy.
 Source: Clinical archive of the National Institute of Pediatrics (N = 63).

100% of the patients had the diagnosis of allergic rhinitis; 74.5% also presented asthma and 6.3% of them also presented atopic dermatitis (See table 1). 19% of the patients presented all three diseases.

Contingency table of patients diagnosed with asthma and atopic dermatitis n = 63					
No Yes		Diagnosis of Atopic Dermatitis		Total	
Asthma Diagnosis	No	Count	15	1	16
		% within Asthma Diagnosis	93.8%	6.3%	100.0%
		% within Diagnosis of Atopic Dermatitis	30.0%	7.7%	25.4%
	Sí	Count	35	12	47
		% within Asthma Diagnosis	74.5%	25.5%	100.0%
		% within Diagnosis of Atopic Dermatitis	70.0%	92.3%	74.6%
Total		Count	50	13	63
% within Asthma Diagnosis			79.4%	20.6%	100.0%
% within Diagnosis of Atopic Dermatitis			100.0%	100.0%	100.0%

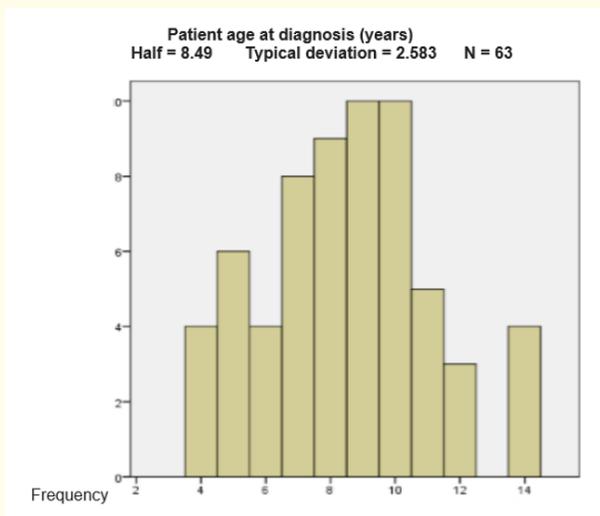
Table 1: Patients diagnosed with asthma and atopic dermatitis.
 Source: Clinical archive of the National Institute of Pediatrics.

The severity of allergic rhinitis presented by patients, according to the classification of the ARIA Guide (Allergic Rhinitis and its Impact on Asthma) 13 First, it was moderate-severe persistent 61.9%, followed by mild persistent 19%, mild intermittent in 15.9% and finally moderate-severe intermittent 3.2% (See graph 2).



Graph 2: Severity of allergic rhinitis according to the classification of the ARIA guide.
Source: Clinical archive of the National Institute of Pediatrics (N = 63).

The average age at which the skin tests were performed and allergy to *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae* was diagnosed was 8.4 years (See graph 3).



Graph 3: Patient's age at diagnosis of mite allergy (years) (N = 63).
Source: Clinical archive of the National Institute of Pediatrics.

The results of the skin tests for 100% positive *Dermatophagoides pteronyssinus* and 98.1% *Dermatophagoides farinae* (See table 2).

Dermatophagoides pteronyssinus skin test			Dermatophagoides farinae skin test	
	Frequency	Percentage	Frequency	Percentage
Positive	63	100	62	98.4
Negative	0	0	1	1.6
Total	63	100	63	100

When comparing the severity of allergic rhinitis with the size of the larger diameter of the papule measured in the positive skin tests for mites, no increasing relationship was found between the two, nor statistical significance (See table 3 and 4).

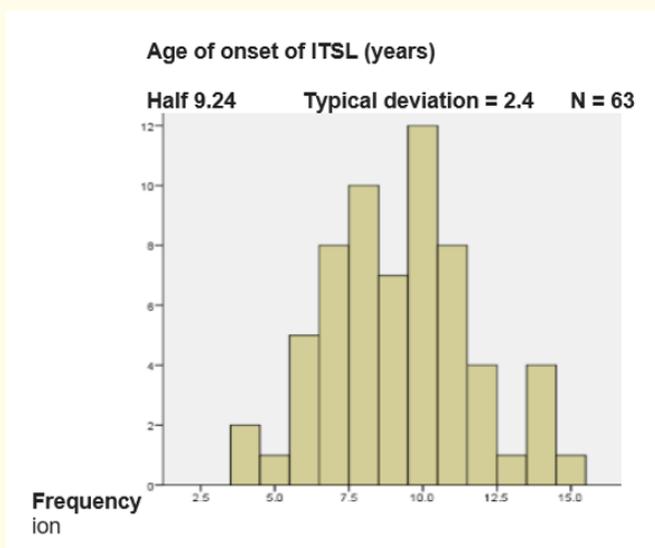
	Severity of allergic rhinitis	N	Half	Student's T
DP papula major diameter	Slight intermittent	10	8.30	4.296
	Mild persistent	12	9.17	3.810
	Moderate-severe intermittent	2	2.50	-0.249
	Moderate-severe persistent	39	31.56	-1.105

Table 3: Comparison of the severity of allergic rhinitis with a larger diameter of the *Dermatophagoides pteronyssinus* papule. Source: Clinical archive of the National Institute of Pediatrics.

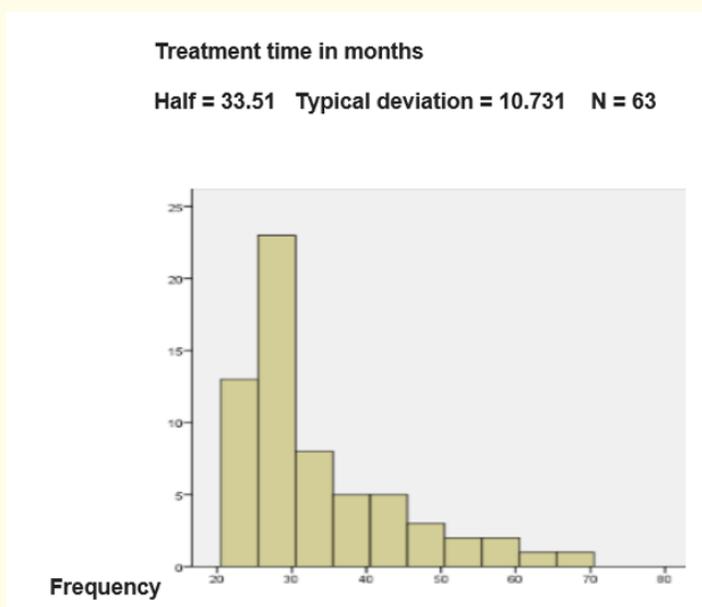
	Severity of Allergic Rhinitis	N	Half	Student's T
Mayor diameter of pápula DF	Slight intermittent	10	7.30	-1.716
	Mild persistent	12	10.33	-1.794
	Moderate-severe intermittent	2	7.50	-0.334
	Moderate- severe persistent	39	54.44	-1.491

Table 4: Comparison of the severity of allergic rhinitis with a larger diameter of the *Dermatophagoides farinae* papule. Source: Clinical archive of the National Institute of Pediatrics.

The mean age of onset of sublingual immunotherapy to mites was 9.24 years (See graph 4), with an average treatment duration of 33.5 months (See graph 5).



Graph 4: Age of onset of sublingual immunotherapy. Source: Clinical archive of the National Institute of Pediatrics



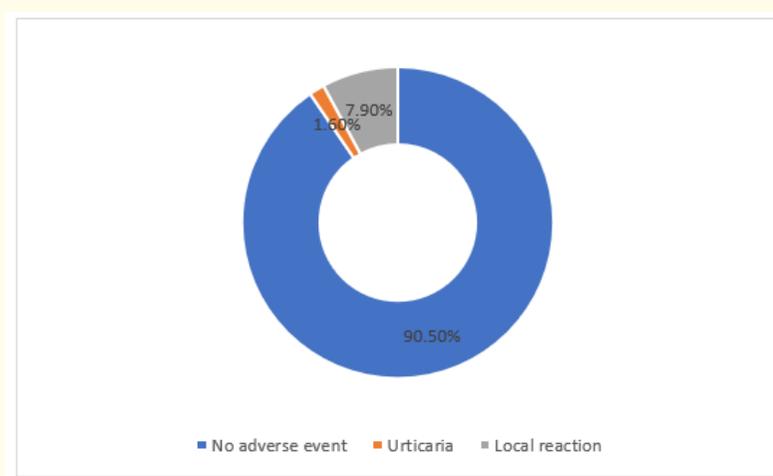
Graph 5: Time of treatment with ITSL against mites.
Source: Clinical archive of the National Institute of Pediatrics.

Regarding the subjective clinical response, before treatment with sublingual immunotherapy, 60 records (95.2%) were registered, of which 56 (88.9%) showed effective results 57.1% presented at some point in the symptomatology of sufficient severity to seek attention in the emergency department. 50.8% had recurrent infections prior to the start of treatment (See table 5).

	Clinical response		Recurrent infections		Emergency assistance	
	Frecuency	Percentage	Frecuency	Percentage	Frecuency	Percentage
Yes	56	88.9	32	50.8	36	57.1
No	4	6.3	31	49.2	27	42.9
Lost	3	4.8	0	0	0	0
Total	63	100	63	100	63	100

Table 5: Clinical response, recurrent infections and emergency assistance.
Source: Clinical archive of the National Institute of Pediatrics.

Of the patients treated with sublingual immunotherapy, 9.5% presented adverse effects, the most common was a local reaction in 7.9% and a 1.6% urticarial reaction (See graph 6).



Graph 6: Adverse effects of sublingual immunotherapy against mites.
Source: Clinical Archive of the National Institute of Pediatrics.

Discussion

The prevalence of allergic diseases has increased considerably in the last 30 - 40 years and in the industrialized world it is estimated that about 25% of all children have some form of allergic problem. Specifically, atopic dermatitis and allergic rhinitis as diseases that typically develop in childhood [7].

In data from the ISAAC study in Mexico, allergic rhinitis affects 8.5% of children aged 6 - 7 years and 16.3% of those aged 13 - 14 years. Regarding asthma, the prevalence is 11.6% in children between 6 and 7 years old, and 13.7% in 13 - 14 years. With respect to atopic dermatitis, these figures range from 2 to 16% in children between 6 and 7 years, and from 1 to 17% in those between 13 and 14 years [8].

Allergic rhinitis and asthma are comorbid diseases: a high percentage of patients with allergic rhinitis (40 - 50%) have asthma, while 80 - 90% of asthmatics have allergic rhinitis [13].

In our study 63 (100%) of the cases presented allergic rhinitis; 74.5% also presented asthma and 6.3% of them also presented atopic dermatitis, 19% of the patients presented all three diseases.

In our cases at the time of diagnosis, the majority of patients presented persistent moderate-severe symptoms (61.9%), followed by mild persistent (19%), intermittent mild (15.9%) and finally moderate-severe intermittent (3.2%).

The age of initiation of treatment with sublingual immunotherapy was on average 9.24 years, which is 10 months higher than the average age of mite allergy diagnosis, this is explained because some of the patients received subcutaneous immunotherapy initially and subsequently decided make the change to sublingual immunotherapy.

The severity of the allergic rhinitis was compared with the size of the larger diameter of the papule against each mite measured in the skin tests, however, no growing relationship was found between them, nor statistical significance, this may be due to the size of the lesion generated in the skin during the test actually relates to the concentration of the allergen in the extract used.

The record of the frequency of administration of ITSL in the file was found only in that of 41.2% of the patients, and on average it was administered 5 days per week, this situation is attributed to the lack of understanding of the patients responsible on the form of administration, since the indication of use is daily to achieve therapeutic doses and therefore greater effectiveness [3].

57.1% presented at some point in the symptomatic condition of sufficient severity to seek care in the emergency department, in one case it was due to urticarial reaction apparently related to the intake of the vaccine, in the rest of the occasions the reason for consultation was due to Present asthmatic crisis.

Sublingual immunotherapy (ITSL) is that it implies easy administration and, according to studies, does not expose users to life-threatening events, serious systemic allergic reactions or events that compromise the airway, the most commonly reported adverse effects are Oral reactions [24]. A study on the safety of STIs in children with asthma found an incidence of mild to moderate adverse effects of 9.6%, with no life-threatening effects, however they report that asthma, hives and rhinoconjunctivitis can occur [31].

This is consistent with our findings on adverse reactions to ITSL, in which 9.5% presented adverse effects, the most common was local oral reaction in 7.9% and there is a report of urticarial reaction in one case, however in the file no the time that elapsed between the administration of the vaccine and the cutaneous manifestations is established, and in the following allergy consultation there was no modification on the dose of sublingual immunotherapy, which makes it doubtful that it has really been treated on a side effect to the administration of the vaccine.

Conclusion

Sublingual immunotherapy against mites is a specific treatment capable of controlling diseases such as allergic rhinitis, asthma and atopic dermatitis, as we find that it efficiently reduces both the symptoms and the need for subjective pharmacological treatment, however we expose an area of opportunity to record these two variables in the service records, as part of the follow-up consultation in order to carry out objective studies on the effectiveness of long-term treatment.

There is no correlation between papule size measured in skin tests with the severity of allergic rhinitis according to the ARIA guideline scale, this is measured to determine the positivity of the study and its size seems to correlate with the concentration of the allergen in the extract used.

We determined the frequency of emergency care of patients with allergic conditions, finding that the main cause is asthmatic crisis, it would be interesting to investigate the percentage of decrease of this once the ITSL against mites began.

Sublingual immunotherapy implies easy administration; we find that it is safe to administer as it did not expose patients to life-threatening adverse events, the most commonly reported adverse effects being local oral reactions.

Within the limitations of this study we found that it was carried out in a third level of care, exclusively in Mexico City, requiring extension studies in other states and countries.

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