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ORIGINAL ARTICLE

Evaluation of the Efficacy and Safety of Sublingual Immunotherapy (Traditional Coca's extract) in Allergic Rhinoconjunctivitis

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ABSTRACT

Background: *Allergic rhinoconjunctivitis is a common allergic disorder that significantly affects the patient's Quality of life (QoL). In countries with low socioeconomic levels, traditional Coca's extracts is an economical choice for Sublingual immunotherapy (SLIT).* ***Objectives:*** *This study aimed to evaluate the efficacy, safety, and effect on medication score of homemade Coca's extracts SLIT in improving the QoL of patients with allergic rhinoconjunctivitis.* ***Methodology:*** *120 allergic rhinoconjunctivitis patients were randomly classified into two similar groups of 60 patients each. Group I received pharmacological therapy regularly, while group II received SLIT and pharmacological treatment. Both groups were followed up for one year.* ***Results:*** *During the period of study, one patient dropped out from group I, while, 9 (15%) patients dropped out from group II. Initially, there were no statistically significant differences in the scores of mini rhinoconjunctivitis quality of life questionnaire (miniRQLQ) or medication scores between the two groups. After one year, both groups showed statistically highly significant improvement in QoL ($p<0.001$); however, improvement in group 2 was statistically significantly higher than group I ($p<0.001$). Medication score of group I showed a mild non-significant decrease from 2.97±0.18 to 2.70±0.723, while, Group II medication score significantly decrease from 3.00±0.000 to 0.38±0.495. There were no severe adverse effects in any of the two groups. No statistical difference was found in the incidence of mild adverse reaction between both groups.* ***Conclusion:*** *Home made Coca's extracts used in SLIT are a safe treatment that improve both qualities of life and medication score in patients suffering from severe allergic rhinoconjunctivitis.*

INTRODUCTION

Allergic rhinitis is a widely spread disease affects 10-40% of the population. It is associated with conjunctivitis in 30%–70% of patients, so it is more appropriately known as allergic rhinoconjunctivitis, in most cases, patients suffer from symptoms that impair the quality of life, these may include: nasal congestion, headache, postnasal discharges, an itchy and runny nose in addition to red, congested watery and itchy eyes.1,2 Uncontrolled allergic rhinoconjunctivitis may also aggravate the symptoms of asthma.[3]

Allergen-specific immunotherapy is known to modify the underlining immunopathological process.[4] It is administered either through the subcutaneous or sublingual route. Although different regimens are available, the principle of treatment includes two phases: build-up phase in which the patient is given increasing amount of allergen extract and maintenance phase during which fixed doses of the highest concentration are given to the patient. The overall duration ranges from three to five years.[4,5] Allergen immunotherapy has also been approved by allergic rhinitis and its Impact on Asthma (ARIA) for adults with moderate to severe diseases.[5,6]

Published literature contains a wide range of sublingual drops, and these formulas need to prove their safety and efficacy.[7]

Egypt is a developing country of a low socioeconomic level.[8] Therefore, homemade Coca's extract represents a suitable economic alternative through which immunotherapy service can be delivered to allergic patients.

Aims of this work were to evaluate the efficacy of homemade Coca's extracts administered as sublingual drops in improving allergic rhinoconjunctivitis patients' quality of life and medication score and investigate the safety of such therapeutic approach.

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METHODOLOGY

Study design

This randomized control study was carried out in Allergy and Immunology Unit, Otolaryngology and Ophthalmology Outpatient's Clinics, Faculty of Medicine, Zagazig University Egypt from June 2017 to October 2018. Patients were randomized in two different groups depending on a blind selection of coloured cards, yellow for group I and green for group II.

Subjects

The study Included 120 patients aged 18 or older. Informed consent was obtained from all participants. Inclusion criteria included a history of moderate to severe chronic allergic rhinoconjunctivitis without any co-morbidities. Diagnosis and scoring of clinical symptoms were based on ARIA guidelines.[9,10] We excluded any patient with active, acute, or chronic obstructive pulmonary disease, patients with severe or unstable asthma, patients whom skin prick testing could not be done (for group II) and Illiterate patients who cannot read the self-administered quality of life questionnaire

Conventional medication used by patients was evaluated on a numerical scale which was: 0 = when medications are not used, 1 = for medications used once a week or less, 2 = medications used 2–3 times per week, 3 = medications used 4 or more times per week**.** [11]

We randomly classified patients into two groups: Group I included patients who received pharmacotherapy only. Group II: included patients who received both sublingual drops plus pharmacotherapy as required.

Questionnaire interview

Quality of life was assessed using the Arabic version of the mini Rhinoconjunctivitis quality of life questionnaire (miniRQLQ). The 14-item mini-questioner included five domains, which are: activity limitation (1, 2, 3), Practical Problems (4, 5), Nose symptoms (6,7,8), Eye symptoms (9, 10, 11) and Other symptoms (12, 13, 14). Patients' response was scored on a 7-point scale, from 0 to 6. Lower scores indicate better QoL. Administration of this self-administered questionnaire was done according to the author's guidelines to ensure the best representation of the patient's quality of life. [12,13]

Each patient was questioned before starting the treatment and after one year of continuing the treatment in either group. The difference in the quality of life between the two questioners was then assessed.

Preparation of allergen Extracts for skin prick testing and Sublingual immunotherapy.

Extracts were prepared as an aqueous solution using the weight/volume (wt/vol) unit which indicates how the extractor vaccine was produced. A potency of 1:100 indicates that 1g of dry allergen was added to 100 cc of a buffer for extraction. The source material was homogenized, blended, crushed, or powdered to produce homogenous slurry for liquid extraction to maximize surface area for contact with the liquid extraction agent. Then acetone was used to remove lipophilic compounds (defatting). Extraction was then done using the allergen extracting fluid comprised from Coca's solution: 5-gram sodium chloride, 2.5-gram sodium bicarbonate, 5-gram phenol crystals and water for injection to make 1000ml water. Following that, the allergens dissolved in the liquid phase were centrifuged for 1 hour to remove non-allergic components. For sterilization of the extract, filtration using filter of 0.22 μιη pore size under complete aseptic condition was done. Filtration was down inside safety cabinet Class II. The filtrate was then collected in sterile bottles. Preparation of dilutions for skin test: Extracts was diluted in 50% glycerin. [14,15]

Standardization of the allergen extract was done using the Nordic Council on Medicines method; briefly, the median concentration of allergen that produces a wheal equal to that of 10mg/ml histamine dihydrochloride is equal to 10000 biological unit (Skin prick testing of 20 consecutive patients was done to detect the median concentration).[16] That concentration was used for subsequent preparations. Only one batch for each allergen was used during the study to ensure consistency. Allergens were stored at 2-8^{0}C with proper labelling.

The Coca's extracted antigens used in the skin prick test were diluted using Glycerin 50% to have a final concentration of 1/10. The test was done according to the recommendations of EAACI; the saline solution was used as negative control and Histamine dihydrochloride (10mg/ml) as a positive control.[17]

The following allergen panel was used (Timothy grass, Rye grass, Chenopodium, Cat hair and dander, Cockroach, Mixed mite (Dermatophagoids farina and Dermatophagoids pteronyssinus), Mixed Feathers (Pigeon, Duck, goose, and chicken) and mixed moulds (Alternaria, Aspergillus, Penicillium, and Cladosporium).

Treatment options:

Group I, received pharmacological treatment of rhinitis according to the ARIA guidelines. Cases of conjunctivitis were dealt with according to American Society for Ophthalmology guidelines.[9] During the period of treatment, follow up was performed as usual. Physical examination and assessment of symptom severity and control were performed.

Group II performed skin prick testing; patients were advised to avoid allergens accordingly**.**[18] Pharmacological therapy was administered as needed. Additionally, this group received sublingual immunotherapy treatment; treatment schedule was divided into two periods; the build-up and maintenance phases.[19] The course of administration was adopted as

the following schedule: the starting concentration was 1:400 for one month with increasing dose of 1 drop for the first ten days then 3 for the next ten days and 5 for the last ten days. A concentration of 1:200 was given for the second month with the same schedule. Followed by another month of 1:100 and then 1:50 for the following month. 1:50 was the maintenance concentration for the remaining period.[20] The schedule of treatment was not fixed; further adjustment was needed for some patients.

Outcome measures:

Patients' compliance/adherence: Patients' reasons for and rate of withdrawal were analyzed. We excluded participants who failed to complete treatment for 12 months from the study. The higher the withdrawal rate is, the lower the compliance.

Patients' quality of life: Improvement in quality of life was assessed by measuring the difference in the scores of the mini RQLQ at the beginning of the study and after completing one year

Evaluation of Safety: any itching or mild swelling in or around the throat, mouth or nose, or any increase of the allergic manifestations was considered as a mild reaction. Additionally, adverse reactions caused by intranasal steroid sprays. Systemic reactions included systemic allergic reaction (anaphylaxis),[21] and systemic adverse reactions of pharmacological therapy.

The difference between Medication scores: medication scores were considered at the beginning and the end of the study.

Statistical analysis

Statistical analysis was performed using SPSS16.0 software (SPASS, Inc., Chicago, IL, USA).

Ethical clearance:

The study was assessed and reviewed by the Zagazig University Institutional Board (IRB) within the ethical consideration in the Declaration of Helsinki and the requirements of national law. The approval number is 4296/18-12-2016. The study was also approved by the Pan African Clinical Trial Registry (www.pactr.org) database. Its unique identification number for the registry is PACTR201901529431463.

RESULTS

Patients' Demographic data

The study started with 120 patients, 60 in group I and 60 in group II. The age of participating cases ranged from 18 to 52 years old in both groups: (66.7%) of patients in group I were males, while the percentage was (70%) in group II. There were no statistically significant differences in age or sex between the two groups (p = 0.99 and 0.70, respectively).

Differences of RQLQ questionnaire and medication scores between both groups at the beginning of the study

Each patient of either arm was given a self-administered mini RQLQ questionnaire form at the time of diagnosis. We found no statistically significant difference between both groups in any of the five categories questioned and subsequently in the total score between the two groups (p-value ranged from 0.06 to 0.69). Additionally, values of medication score were similar for both groups at the start of the study (p = 0.16). (table 1).

Table 1: Results of RQLQ questioner and medication scores of both groups at the beginning of the study

At the beginning of the study		N	Mean	SD	Median	range		MW	*P*
Activity	Group 2	60	7.98	5.020	7	0	18	1.96	0.06
	Group 1	60	8.55	3.643	8	2	15		NS
Practical problems	Group 2	60	8.50	2.949	9	3	12	1.97	0.06
	Group 1	60	7.98	2.600	8	2	12		NS
Nose symptoms	Group 2	60	11.17	5.340	12.5	0	18	0.55	0.59
	Group 1	60	11.13	4.394	12	1	18		NS
Eye symptoms	Group 2	60	8.43	5.457	9	0	18	0.40	0.69
	Group 1	60	8.77	4.795	9	2	18		NS
Others	Group 2	60	9.35	4.683	9	0	18	1.38	0.17
	Group 1	60	10.55	4.196	10	3	18		NS
Total	Group 2	60	45.05	16.338	39	22	78	0.72	0.47
	Group 1	60	45.35	11.967	40.5	19	71		NS
Medication score	Group 2	60	3.00	0.000	3	3	3	1.43	0.16
	Group 1	60	2.97	0.18	3	2	3		NS

NS, statistically non-significant

Skin prick testing in group 2 patients

Skin Prick test was performed for patients in group II only, as a prerequisite for initiation of SLIT. Results of skin Prick test revealed that mixed mite allergen (*D. farina* and *D. pteronyssinus*) was by far the most common allergen among patients. Followed by mixed feather; meanwhile, the least common allergen against which patients were sensitized was cat hair and dander (figure 1).

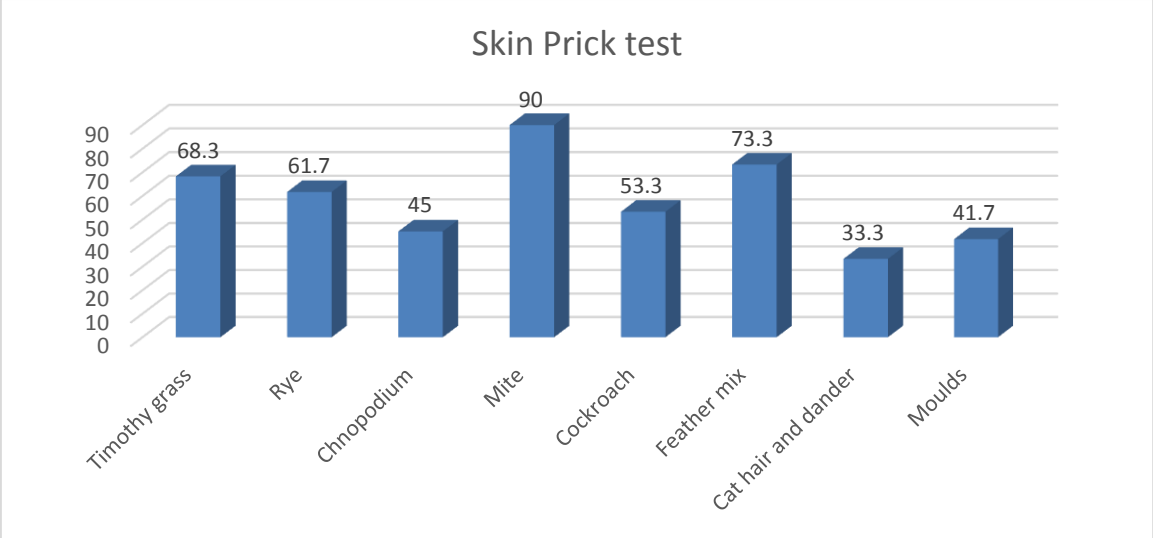

Fig. 1: Results of Skin prick testing in group 2 patients

Causes of cases dropped out of the study.

After one year of follow up, only one patient was dropped out from group I due to lost connection, while nine patients dropped out from group II. Causes of withdrawal in group II included, improvement of symptoms (3 patients), lost contact (2 patients). Four patients had misconception regarding the value and effect of immunotherapy.

RQLQ and medication score of group I at the beginning and the end of the study

Regarding group I, after one year of pharmacological treatment, there were significant improvements in most aspects of QoL. However, no improvement was detected in the medication score (table 2).

Table 2: RQLQ and medication score of group I at the beginning and the end of the study

	activities	Practical problems	Nose symptoms	Eye symptoms	others	Total	MS
Paired Wilcoxon	3.545	2.23	3.43	4.768	4.373	3.979	1.96
P	<0.001**	0.01 NS	0.001**	<0.001**	<0.001**	<0.001**	0.06 NS

NS, statistically non significant; *P <0.05 statistically significant; ** P <0.001 highly statistically significant, MS medication score

RQLQ and medication score of group II at the beginning and the end of the study

Regarding group II, after one year of SLIT and as needed pharmacological treatment, there was a significant improvement in all aspects of QoL and the medication score (table 3).

Table 3: Comparing values of mini RQLQ at the beginning and the end of the study in Group 2:

	activities	Practical problems	Nose symptoms	Eye symptoms	others	Total	MS
Paired Wilcoxon	4.118	4.059	4.148	3.027	3.799	4.169	4.443
P	<0.001**	<0.001**	<0.001**	0.002**	<0.001**	<0.001**	<0.001**

** *P* <0.001 highly statistically significant, MS medication score

Differences of RQLQ questionnaire and medication scores between both groups at the end of the study

After 12 months, 51 patients in group II and 59 patients of group I were reassessed using the same RQLQ mini questionnaire and the same medication score. There were highly statistically significant differences between both groups regarding all individual items of RQLQ, total questionnaire score and medication score (*p* ranged from <0.001 to 0.006) (table 4).

Table (4): Results of RQLQ questioner and medication scores of both groups at the end of the study.

		N	Mean	SD	Median	range		MW	P
Activity	Group 2	51	1.17	1.193	1	0	4	5.55	<0.001**
	Group 1	59	5.88	3.540	6	1	15		
Practical problems	Group 2	51	2.61	2.251	2	0	11	4.32	<0.001**
	Group 1	59	6.02	3.642	4	2	12		
Nose symptoms	Group 2	51	2.87	2.418	3	0	11	3.90	<0.001**
	Group 1	59	6.93	4.881	6	1	18		
Eye symptoms	Group 2	51	2.13	2.581	1	0	11	2.75	0.006**
	Group 1	59	4.28	4.261	3	0	18		
Others	Group 2	51	3.96	2.440	3	2	10	1.98	0.04*
	Group 1	59	6.05	4.810	5	1	18		
Total	Group 2	51	12.30	8.331	10	4	42	5.18	<0.001**
	Group 1	59	29.26	18.020	24	11	73		
Medication score	Group 2	51	0.38	0.495	0	0	1	8.76	<0.001**
	Group 1	59	2.70	0.723	2	1	3		

**P* <0.05, statistically significant; ** *P* <0.001, highly statistically significant

Side effects and Safety

There were no serious adverse effects observed during therapy in any of the two groups. Nevertheless, few mild adverse reactions, including oral itching, exacerbation of allergic manifestations and mild dizziness have been reported in both groups which have disappeared with continuing treatment.

DISCUSSION

Allergy and Immunology Unit, Faculty of Medicine Zagazig University, is a regional unit, serving patients of Sharkia governorate with a population of over sixand a half million in 2016.[22] Based on previous data suggesting that Allergic rhinoconjunctivitis affects about a fifth of the general population[23]. A considerable number of patients can be expected. Unfortunately, due to compromise financial conditions and failure, till now, to have the immunotherapy included in the national health insurance service, using the ready made commercially prepared allergens formulates an unaffordable economic cost for most patients. As a result, home made crude allergen Coca's extracts represent the ideal solution for both skin prick testing and desensitization schedules.

At the beginning of the study, there was no detectable difference between the QoL of the two studied groups as measured by the miniRQLQ questionnaire. This was applicable for each of the five categories and also the total value. Similarly, values of medication scores were high in both groups.

Our results for skin prick testing showed that 90% of patients were sensitized to house dust mites, followed by 73% for mixed feather, 68.3% for timothy grass and 61.7% for rye grass. The least was 33.3% for cat dander and hair. House dust mite is known to be a significant allergic reaction driving allergen.[24] Feathers and grass exposure are identical for the patient's environmental exposure as most of the sharkia governorate's inhabitants are farmers or at least live in agriculture areas. Mixed moulds are another major allergen that is

strongly related to environmental conditions.[25] A previous study in Egypt showed that the prevalence of fungal allergic diseases is higher in Egypt due to its climatic conditions compared to colder countries.[26]

Adherence to the treatment regimen is a crucial issue as it ensures the maximum benefit for the patient. Relatively, a long duration is needed to complete the course of immunotherapy (from 3 to 5 years).[24] According to our study, nine patients (15 %) from group II and one patient from group 1 quitted from the study; other studies found that the drop out rates ranged from 49% to 82%.[37] Causes of no adherence in group II were variable; the most important was the improvement of the allergic symptoms. Although it is expected that the patient's sense of improvement will drive him/her to continue the treatment as required, three patients stopped the treatment as soon as their symptoms relieved. However, we had utterly clarified the value of completing the whole course of treatment. Two patients changed their accommodation to other distant governorates or travelled out of Egypt, as the immunotherapy has to be given only in the unit, continuing the treatment was inconvenient. The interesting point was that two patients quitted the treatment because of being advised against immunotherapy from non-specialized personnel. Two patients were convinced that the SLIT is inefficient, and the other two thought the treatment might result in serious side effects for their infants (two female patients got pregnant during treatment. They choose to stop SLIT despite our clarification that SLIT is effective, and safe during pregnancy.[28]

Several studies have investigated causes of non-adherence in the settings of immunotherapy; they yield different results like non-perception of efficacy, side effects, and costs.[29,30] It is expected to have a full range of non-adherence causes, as this is mostly dependent on the population's culture and socioeconomic status.

For both lines of treatment, there was a highly significant improvement in most aspects of Quality of life assessed by the given questionnaire for group I and all aspects for Group II.

When we compared the results of miniRQLQ between the two groups, we found highly statistically significant improvement in patients receiving SLIT than those receiving pharmacological therapy only. This clarifies that SLIT is more superior than pharmacological therapy alone in improving QoL in patients suffering from moderate to severe allergic rhinoconjunctivitis. Other studies have proved the efficacy of SLIT in improving the Quality of life of a patient with allergic rhinoconjunctivitis. From another hand, the effectiveness of the home made cost-effective Coca's extract is comparable to other studies that used the more expensive commercially available extracts. [31, 32, 33,34]

Medication score is another important aspect of evaluation, although patients of both groups had a similar medication score at the start of the study with no statistical difference. This study found a highly significant improvement of the medication score in a patient receiving SLIT than those who were dependent on the pharmacological treatment only. This result could be attributed to the role of immunotherapy in modulating the immunopathological events resulting in allergy comparing with the pharmacological therapy, which deals with the final products of allergic process and aims to improve the symptoms.[35]

Safety of treatment is an essential aspect of evaluation; fortunately, no serious adverse effect, for example, anaphylactic shock, laryngeal or oropharyngeal edema has been recorded in any of the two groups. However, the most common side effect was the exacerbation of the allergic symptoms; this could be alleviated by modulating the treatment regimen, other mild adverse effects like oral itching disappeared with continuing therapy. Adverse effects of SLIT have been a hot issue in several pieces of research where the treatment has proven to safe.[36]

According to our knowledge, this is the first study to consider the effect of SLIT on in improving QoL and medication score in Egyptian patients. We hope that this study will help in bridging the gap of the scarcity of information regarding allergic diseases in Egypt and other developing countries.

CONCLUSION

SLIT using home made Coca's extracts is an effective and safe line of treatment for patients suffering from allergic rhinoconjunctivitis. It causes not only marked improvement in patients' QoL, but it is also safe and significantly decreases the need for pharmacological therapy.

- The authors declare that they have no financial or non financial conflicts of interest related to the work done in the manuscript.
- Each author listed in the manuscript had seen and approved the submission of this version of the manuscript and takes full responsibility for it.
- This article had not been published anywhere and is not currently under consideration by another journal or a publisher.

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