A nasally applied cellulose powder reduces symptoms of seasonal allergic rhinitis (SAR). A double blind, placebo controlled trial in children and adolescents.

Åberg N and Benson M
Sahlgren's Academy, University of Gothenburg, The Queen Silvia Children's Hospital, Gothenburg, Sweden

Corresponding Author:
Dr Nils Åberg
The Allergy Clinic
The Queen Silvia Children's Hospital, SE-416 85 Gothenburg, Sweden
e-mail: nils.aberg@vgregion.se

Abstract

Background: A nasally applied cellulose powder has been increasingly used in many countries as a remedy for allergic rhinitis. The absence of side effects makes the treatment particularly attractive in children. In adults, one previous controlled trial demonstrated a reduced use of rescue medication but no reduction of symptoms.

The aim of this study was to evaluate the efficacy in pollen allergic children.

Methods: A double blind, placebo controlled study was conducted in 53 children with allergic rhinitis aged 8-18 years over the birch pollen season of 2009. Allergy to birch pollen was confirmed by a blood test. The patients were assigned randomly to two groups (A, Active and P, Placebo). All children were given an antihistamine dose daily, and supplied with a mobile phone for instructions, daily reminders and reporting symptom scores, by SMS.

Results: Very good compliance was obtained. Intention to treat analysis showed a significant reduction of total symptom scores from the nose (P 7.29, A 6.07, p=0.033) and specifically for runny nose (P 2.56, A 2.03, p=0.017). All symptoms from the nose, eyes and lower airways were lower in the active group but reached significance only as above. The best effect was seen during a rainy week with lower pollen counts. No clinically significant adverse effects were seen.

Conclusions: The cellulose powder reduces symptoms of SAR in children and adolescents and may be effectively combined with oral antihistamine treatment. SMS communication on a mobile phone for reminders and recording symptoms is an excellent reporting tool.

Introduction

Allergic rhinitis appears to have increased in Sweden as well as in most affluent societies over the 20th century [1, 2]. During childhood and adolescence the prevalence of allergic rhinitis increases with age [3]. In school children allergy to pollen is a predominant cause [4]. Apart from notable economic costs many school children experience an adverse impact on their educational career [5]. A range of remedies and treatments are available on prescription and over the counter. Some of these may have adverse effects and the relief is very often insufficient. Nasal steroid sprays are considered as the most efficacious but many sufferers are reluctant to take them due to fear of adverse effects.

An inert cellulose powder (Nasaleze®) has been on sale as a medical device against hay fever in Europe since 1994. It is applied in the nostrils by a simple puffer device. The mechanism of action of the cellulose is likely to be a reaction with moisture on the mucous membrane. A protective barrier on the nasal mucosa may prevent contact between inhaled allergen and mucosal cells. One placebo controlled clinical trial in adults with grass pollen allergy showed a reduced need of rescue medication but no significant symptom relief [6]. The inert substance has been virtually free from adverse effects, making it a particularly attractive treatment option for children. Still, no controlled clinical studies in children have been performed. Our aim was to assess the efficacy in a common clinical setting along with an oral antihistamine. In Sweden, birch pollen allergy is the most common cause of SAR. Furthermore, the birch pollen occurs during a school term and yearly examinations with high risks of interference between symptoms of SAR and school results [5]. Therefore, we found it particularly important to study the efficacy in birch pollen induced SAR in children.

Methods

Research design:
Patients 8-18 years old were recruited by newspaper advertising during February-April 2009. They all had a history of typical symptoms of SAR during springtime. They should not have used nasal steroids. At an appointment the history was scrutinized and an assessment of the severity excluded a current need for nasal steroids. They were tested with a finger prick blood sample for ImmunoCap Rapid (Phadia). ImmunoCap Rapid is an in vitro system with immediate results for the most common respiratory allergies with a high accuracy regarding both sensitivity and specificity [7, 8]. Fifty two children tested positive for birch pollen allergy. One child tested negative in the blood sample but with a strongly positive history and a positive skin prick test for birch pollen allergy during the same month the child was also included in the study. The patients were randomly assigned to active (A) or placebo (P) treatment 3 times daily from an identical container. The nasal powders were supplied in patent approved plastic containers which deliver the powder from a nozzle when squeezed. The exact amount delivered is not standardized and the variations of patterns of deposition in the nose are not known. The placebo was a lactose powder with the same particle size, appearance and the same tinge of mint taste as the cellulose powder. The containers were labelled with serial numbers. The randomisation codes for active and placebo products were not revealed until the reported scores had been locked in a clean file at the end of the study. After the study was completed all participants were informed whether they had taken the active or placebo products.

All children were given one Desloratadine orally soluble tablet in a dose appropriate for age once daily during the treatment period. Each child was supplied with a mobile phone for instructions, reminders and reporting of symptoms, all by SMS. The medication and reporting lasted for 4 weeks following the first increase of local birch pollen counts.

3 times a day the patients were reminded by SMS to take their treatment including the nasal puffs and were asked to confirm the intake by a response SMS. At the evening reminder, they were asked about the severity of symptoms during the preceding day from the nose, eyes and lower airways and to answer with a figure 1-6. The figure *1* corresponded to "*no trouble at all", 2"little trouble", 3"moderate trouble",* 4*"rather much trouble", 5"much trouble",* and *6* "*very much trouble" respectively*. From the nose, scoring of sneezing, running nose and blocked nose were reported. For the eyes and lower airways, respectively, only a concluding figure was used. Otherwise the SMS-procedure was assumed to be too complicated and time consuming for the children.

Statistical methods

For each question the mean score was calculated for the whole 28 days period for every child. Mean values for the sum of all scores as well as the sum of the nasal scores were also calculated. The two treatment groups were then compared using t-tests. All results were based on intention to treat analyses. P-values below 5% were considered significant. Days with a pollen count above and below 100/m^3 and day, respectively, were separated and analysed in the same way as the whole period.

The study was approved by the ethics committee at the Sahlgren's Academy of the University of Gothenburg.

Results:

All patients lived within an area of 30 kilometres from the study centre. Pollen samples were collected on the roof of an adjacent hospital building, using a Burkard 7-day volumetric spore trap. The counts are representative for a wide area with a radius of ca 50 km from the trap. The birch pollen season 2009 was intense but not a record high, viz. 163% of the local mean of the annual pollen sum. The local birch flowering started one week before the study beginning on April 21 with maximum of 3,700 pollen/m^3/day on April 25 (Åslög Dahl, Botanical Analysis Group Ltd, Gothenburg)

An excellent compliance was obtained. Only 6% of all possible SMS-replies were missing, including one boy who withdrew because of throat irritation. One girl used nasal steroid as rescue medication for one day. Both belonged to the placebo group and are included in the intention to treat analyses. There were 25 children in group A and 28 in group P. The gender distribution was 3/2 in favour of boys in both groups. The mean age was 11 in both groups. No clinically significant adverse effects were reported. A total of 8 children evenly distributed between the groups experienced some irritation in nose or throat.

Table 1 shows symptom scores over the entire 4 weeks with a general tendency to reduction of all symptoms from nose, eyes and lower airways in the active group. The mean scoring for nose and eyes ranged between 2 (”little trouble”) and 3 (”moderate trouble”). There was a significant reduction of total symptom scores from the nose (P 7.29, A 6.07, p=0.033) and specifically for running nose (P 2.56, A 2.03, p=0.017).

Table 1. Total of symptoms scored retrospectively at night for 4 weeks

Alla dagar

Question	Treatment	n	Mean	p-value
Sneezing	Placebo	28	2.31	0.060
	Active	25	1.91	
Running nose	Placebo	28	**2.56**	**0.017**
	Active	25	**2.03**	
Blocked nose	Placebo	28	2.42	0.24
	Active	25	2.13	
Eye symptoms	Placebo	28	2.26	0.53
	Active	25	2.11	
Lower airways	Placebo	28	1.63	0.48
	Active	25	1.47	
Sum of all symptoms	Placebo	28	11.17	0.097
	Active	25	9.66	
Sum of nasal symptoms	Placebo	28	**7.29**	**0.033**
	Active	25	**6.07**	

Figure 1 illustrates the relation between symptom scores and pollen counts. Visually there was a lag of 2 days between changes in pollen counts and subsequent symptoms. The best effect of the treatment was seen after lower pollen counts.

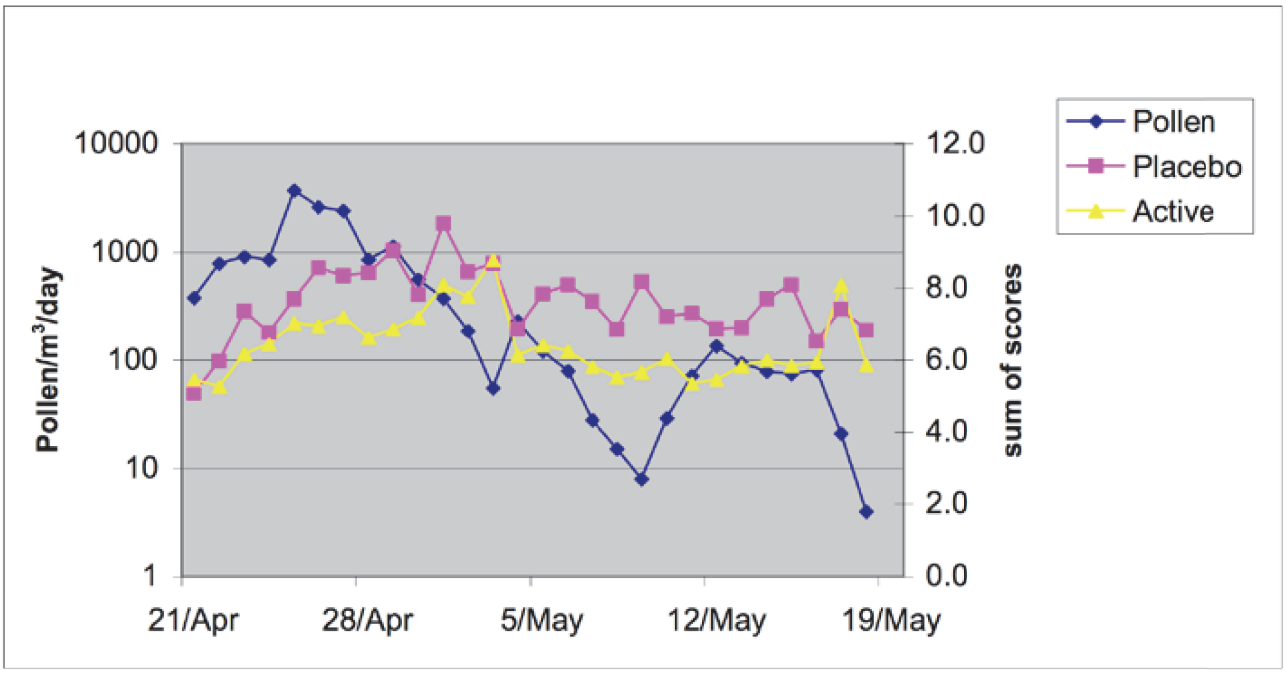


Table 2 shows an increased difference in mean scores between the groups with low pollen counts (<100 pollen/m^3/day) as compared with higher pollen counts with a significant reduction also of sneezing severity.

Table 2. Sum of symptoms scored retrospectively at night
a) 2 days after pollen counts <= 100/m^3

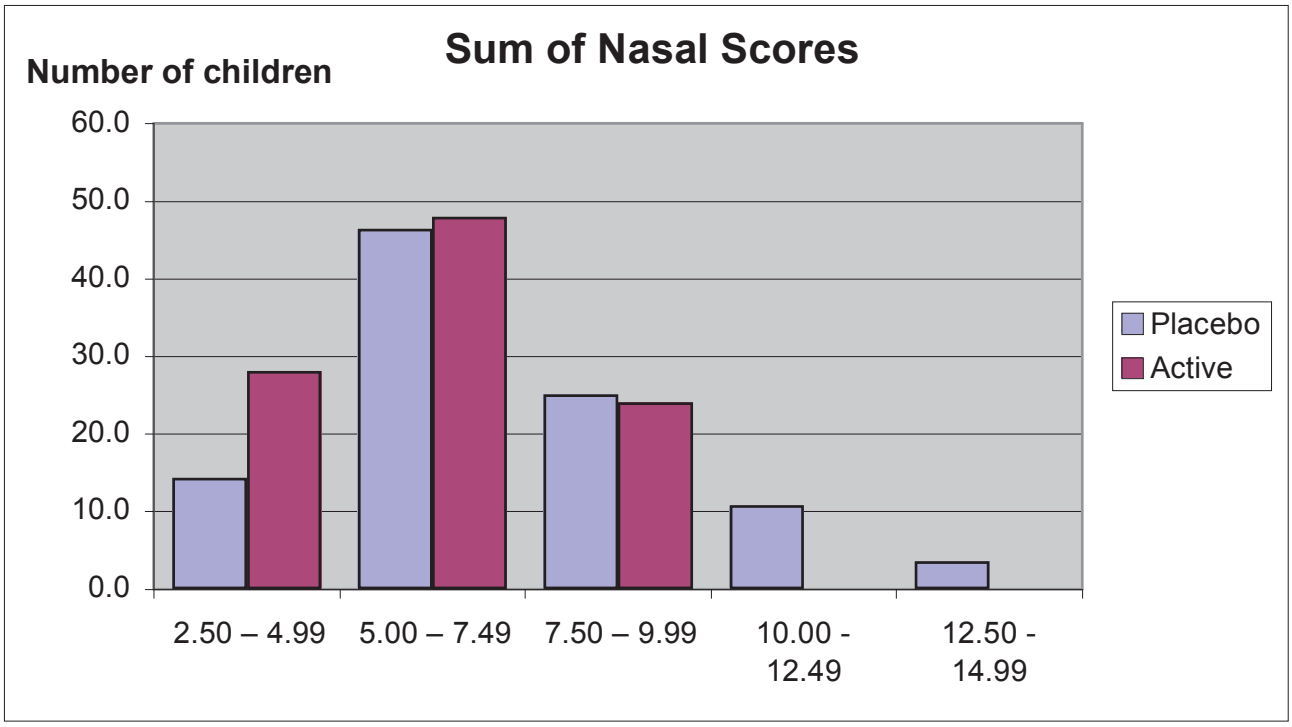
Question	Treatment	n	Mean	p-value
Sneezing	Placebo	27	**2.19**	**0.023**
	Active	25	**1.65**	
Running nose	Placebo	27	**2.35**	**0.019**
	Active	25	**1.79**	
Blocked nose	Placebo	27	2.21	0.23
	Active	25	1.88	
Eye symptoms	Placebo	27	1.79	0.84
	Active	25	1.75	
Lower airways	Placebo	27	1.59	0.51
	Active	25	1.45	
Sum of all symptoms	Placebo	27	10.14	0.081
	Active	25	8.50	
Sum of nasal symptoms	Placebo	27	**6.75**	**0.025**
	Active	25	**5.32**	

b) 2 days after pollen counts > 100/m^3

Question	Treatment	n	Mean	p-value
Sneezing	Placebo	28	2.39	0.15
	Active	25	2.08	
Running nose	Placebo	28	**2.67**	**0.038**
	Active	25	**2.19**	
Blocked nose	Placebo	28	2.56	0.29
	Active	25	2.27	
Eye symptoms	Placebo	28	2.50	0.52
	Active	25	2.33	
Lower airways	Placebo	28	1.63	0.54
	Active	25	1.50	
Sum of all symptoms	Placebo	28	11.75	0.15
	Active	25	10.37	
Sum of nasal symptoms	Placebo	28	7.62	0.074
	Active	25	6.54	

In Figure 2 the distribution of severity scores is deviated to milder disease in treatment group with a virtual eradication of the most severe symptoms.

		Treatment		Treatment	
		Placebo	Active	Placebo	Active
Sum of Nasal Scores	2.50 – 4.99	4	7	14.3	28.0
	5.00 – 7.49	13	12	46.4	48.0
	7.50 – 9.99	7	6	25.0	24.0
	10.00 – 12.49	3	0	10.7	0.0
	12.50 – 14.99	1	0	3.6	0.0
Total		28	25	100.0	100.0



Discussion

Since 1994 this British remedy for hay fever has been on sale as a medical device and it has been increasingly used in many parts of the world. The inert cellulose powder has in various previous studies, mainly in adults, been free from clinically significant adverse effects [6, 9, 10]. The safety aspect of the product makes it particularly attractive for treatment of children. This is the first placebo controlled study in children in a clinical setting. It is also the first placebo controlled study of the product proving a reduction of symptoms of SAR. In adults with grass pollen rhinitis their was a reduction of rescue medication but no decrease in symptom scores [6]. We wanted to avoid that variation in other treatments that obscured the efficacy of the trial product. Therefore, we chose a fixed oral antihistamine dose throughout the study period, which is a common clinical context.

Another original feature with the study was the use of SMS logistics for reminders and reporting of symptom scores. This arrangement probably explains an unusually high compliance in this age group. Some concern from the study staff regarding the SMS skill of the children (asking for SMS interest in the advertisement) was rudely mocked by the children at the first appointment.

The main weakness of the study is the relatively small number of patients. Consequently, most of the general reduction of all symptoms did not reach statistical significance. The smaller the number of patients, the greater is also the risk of selection bias regarding differences in preceding severity between the groups. A baseline symptom registration should have been gathered in order to meet this question. The time schedule of the trial, however, did not allow for such a measure. Furthermore, the total study population was quite homogenous with a narrow range of severity, no history of asthmatic or other perennial symptoms and no previous use or assessed need of nasal steroids was allowed at inclusion. This background ought to minimise the risk of significant baseline group differences.

The profile of the effects with the predominating and statistically significant reduction of nasal symptoms is suggestive of a real biological effect. A less pronounced relief of ocular and bronchial symptoms may be secondary to the nasal effects in line with the concept of “united airways” [12]. The number of patients, however, did not allow for statistical significance of the reduction of non-nasal symptoms. Still, the consistent reduction of all symptoms may support the notion of a biological sequence of effects.

The choice of birch pollen rhinitis in the study was firstly that it is the most common cause of SAR in Swedish children [4]. Secondly, for children with multiple pollen allergies, birch pollen symptoms usually are the first of the total season. In severe birch pollen allergy patients often have a cross reaction to hazel and alder earlier in spring time. Already at recruitment, however, we excluded children with perennial allergic symptoms or seasonal symptoms in the months preceding birch flowering. We believe that absence of all symptoms previously in the same year may have contributed to a narrow range of severity. Most children in Sweden with grass pollen allergy also have a birch pollen allergy [4] and the baseline condition in a study of grass pollen allergy would have been more heterogeneous.

The magnitude of reduction of nasal symptoms in the trial of 20-25% was less than might have been expected from the clinical experience of the authors. Still, it corresponded to the cautious power calculations preceding the clinical part of the study. In clinical practice the dosage is usually 2-3 times daily under ordinary pollen exposure but with a possibility to increase the doses as required. The birch pollen levels in Sweden in the present study were much higher than for instance the grass pollen levels in the previous study of the product on grass pollen allergy in UK [10]. The assumed mode of action of the cellulose powder is to form a gelatinous barrier preventing contact between pollen and the mucous membrane. It may be a matter of course that intense exposure may result in breakthrough of sneezing and running nose with blowing out of the powder/gel and subsequent absence of powder and effect. Such a sequence may be part of a dose-response relationship between the frequency of doses and efficacy. In the previous grass pollen study on the product [10] the dose was mainly once daily and this low dose may have contributed to the shortage of symptom reduction.

We appraised a fixed dose of 3 times daily to be convenient and necessary to maintain controlled circumstances in our trial design. Still it may not have been an optimal setting to prove the real efficacy of the product during a period of high pollen counts. Thus, the average symptom scores in the treatment group can be assumed to result from quite a wide scope of effects from very good to complete absence of effects. The concurrent fixed antihistamine dosage probably alleviated the breakthrough of pollen peak symptoms, but may also have constricted the range of scoring available for reduction after lower pollen counts. Given the aim of extensive symptom relief, our impression still is that the antihistamine treatment left a substantial need for further aid.

The optimal frequency of puffing the powder into the nostrils to obtain a 24 h protection of mucous membranes remains unknown and, as discussed above, may vary with amount of allergen exposure. The ordinary clearance time of the nasal mucosa of less than 30 minutes is prolonged for cellulose products, a fact that may be used for certain treatment purposes [13]. Another gel formulation from sea water was efficacious against allergic rhinitis in a 4 times daily regimen in a recent study [14]. The higher efficacy in the lower pollen range may support our clinical impression that a three time's daily dose may be sufficient.

In conclusion, we demonstrated that an inert cellulose powder (Nasaleze®) causes a significant protection or alleviation of nasal symptoms in SAR in children. All symptoms from upper and lower airways were reduced but only the reduction of symptoms from the primary target of the treatment, the nose, reached significance. A fixed dosage of 3 applications daily was sufficient but probably not clinically optimal during very high pollen exposure. The product can be combined with use of oral antihistamine, the most common treatment of SAR [10]. The complete safety of the formulation was confirmed. A novel logistics tool was introduced in the study; SMS-logistics providing reminders and registration of symptom scores which appeared to be a promising concept for clinical trials.

Acknowledgements

Kisska International Ltd and Green Medicine AB sponsored the study in terms of supplying test products, support of the logistics including mobile phones and funding for the nursing staff.

We are grateful to the registered nurses Kerstin Sandstedt and Mainor Åmark for skill patient contact and testing and to senior lecturer Lars Wahlgren, University of Lund, for statistical analyses.

References

[1] Aberg N. Asthma and allergic rhinitis in Swedish conscripts. Clin Exp Allergy. 1989; 19: 59-63.

[2] Aberg N, Hesselmar B, Aberg B, Eriksson B. Increase of asthma, allergic rhinitis and eczema in Swedish schoolchildren between 1979 and 1991. Clin Exp Allergy. 1995; 25: 815-9.

[3] Aberg N, Engström I. Acta Paediatr Scand. Natural history of allergic diseases in children. 1990; 79: 06-11.

[4] Hesselmar B, Aberg B, Eriksson, Aberg N. Allergic rhinoconjunctivitis, eczema, and sensitization in two areas with differing climates. Pediatr Allergy Immunol. 2001;12: 208-15.

[5] Sundberg R, Torén K, Höglund D, Aberg N, Brisman J. Nasal symptoms are associated with school performance in adolescents. J Adolesc Health. 2007; 40:581-3. Epub 2007 Apr 12.

[6] Emberlin JC, Lewis RA. A double blind, placebo-controlled cross over trial of cellulose powder by nasal provocation with Der p1 and Der f1. Curr Med Res Opin. 2007 Oct;23(10):2423-31.

[7] Diaz-Vazquez C, Torregrosa-Bertet MJ, Carvajal-Urueña I, Cano-Garcinuño A, Fos-Escrivà E, García-Gallego A, López-Cacho F, Monzón-Fueyo MC, Pérez-Porcuna XM, Accuracy of ImmunoCAP Rapid in the diagnosis of allergic sensitization in children between 1 and 14 years with recurrent wheezing: the IReNE study. Ridao-Redondo ML.Pediatr Allergy Immunol. 2009; 20:601-9.

[8] Eigenmann PA, Kuenzli M, D'Apuzzo V, Kehrt R, Joerg W, Reinhardt M, Rudengren M, Borres MP, Lauener RP. The ImmunoCAP Rapid Wheeze/Rhinitis Child test is useful in the initial allergy diagnosis of children with respiratory symptoms. Pediatr Allergy Immunol. 2009; 20: 772-9.

[9] Josling P, Steadman S.Use of cellulose powder for the treatment of seasonal allergic rhinitis. Adv Ther. 2003 Jul-Aug;20(4):213-9.

[10] Emberlin JC, Lewis RA. A double blind, placebo controlled trial of inert cellulose powder for the relief of symptoms of hay fever in adults. Curr Med Res Opin. 2006; 22: 275-85.

[11] Lauritsen K, Degl' Innocenti A, Hendel L, Praest J, Lytje MF, Clemmensen-Rotne K, Wiklund I.Control Clin Trials. Symptom recording in a randomised clinical trial: paper diaries vs. electronic or telephone data capture. 2004 Dec;25(6):585-97.

[12] Braunstahl GJ. United airways concept: what does it teach us about systemic inflammation in airways disease? Proc Am Thorac Soc. 2009 Dec;6(8):652-4.

[13] Griesenbach U, Meng C, Farley R, Wasowicz MY, Munkonge FM, Chan M, Stoneham C, Sumner-Jones SG, Pringle IA, Gill DR, Hyde SC, Stevenson B, Holder E, Ban H, Hasegawa M, Cheng SH, Scheule RK, Sinn PL, McCray PB Jr, Alton EW. The use of carboxymethylcellulose gel to increase non-viral gene transfer in mouse airways.
Biomaterials. 2010 Mar;31(9):2665-72. Epub 2009 Dec 21.

[14] Cingi C, Halis Unlu H, Songu M, Yalcin S, Topcu I, Cakli H, Bal C. Seawater gel in allergic rhinitis: entrapment effect and mucociliary clearance compared with saline. Ther Adv Respir Dis. 2010 Feb;4(1):13-8. Epub 2009 Dec 30.