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Comparative Evaluation of the Efficacy in Treating Children with Seasonal Allergic Rhinitis Using Antihistamine Combined with Ectoine Nasal Spray and Antihistamine Monotherapy: Results of an Open Randomized Study.

***Objective**: Our aim was to evaluate the efficacy of an ectoine nasal spray in treating children with seasonal allergic rhinitis. **Methods**: An open randomized study of children aged 3–17 with the aggravation of early spring hay fever. All participants received oral antihistamine, and the children of the treatment group — oral antihistamine plus ectoine nasal spray. The symptoms of the disease and the amount of additional drug therapy were analyzed on the 1st, 10th and 21st day of treatment. **Results**: The group with patients who received an ectoine nasal spray (n = 24) showed a significant, if compared to the control group (n = 18), decrease in the severity of all symptoms of rhinitis — nasal congestion from the 14th day of treatment (p = 0.010), nasal discharge — from the 15th day of treatment (p = 0.036), nasal irritation and sneezing — from the 17th day of treatment (p = 0.020), as well as the symptoms of allergic conjunctivitis such as itchy eyes — from the 18th day of treatment (p = 0.020) and conjunctival hyperemia — from the 19th day of treatment (p = 0.040). The use of an ectoine nasal spray was accompanied by a decrease in the frequency of the assignment of drugs for the additional rhinitis treatment. **Conclusion:** An ectoine nasal spray in combination with antihistamines induces a more rapid relief of major symptoms of seasonal allergic rhinitis and allergic conjunctivitis in children, as well as reduces the need for additional medical treatment of the disease, if compared to the antihistamine monotherapy.*

***Key words**: children, hay fever, allergic rhinitis, treatment, nasal spray, ectoine.*

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RATIONALE

According to the results of national and international studies, allergic rhinitis is a widespread allergic pathology that invaded the upper respiratory tract. The incidence of this allergic disease type has a tendency to grow [1]. Pollen is the main trigger for allergic reactions which cause the seasonal form of allergic rhinitis. Pollen allergen exposure causes the increase in the number of eosinophils in the nasal mucosa leading to severe symptoms of the disease [2, 3].

During the treatment of seasonal rhinitis in children it is recommended to avoid exposure to cause-significant allergens. [4] In practice, the following measures can be helpful: moving to a different climate zone for the period of exacerbations, using filters or protective films for nose, staying indoors (accommodations should be equipped with air filter systems), nasal saline irrigation [5–7]. Isotonic saline solutions for mold elimination and moistening the nasal mucosa

are optimal for preservation of the mucociliary apparatus function. Moreover, its osmotic composition is similar to blood plasma [8].

To improve the procedure of allergen elimination, the application of ectoine, a natural compound found in extremophiles – micro-organisms that thrive in extreme environments, was proposed [8]. Ectoine accumulates water molecules on the surface of the mucous membrane forming a "hydration shield" that protects the mucosa from adverse environmental conditions including the exposure to allergens. Importantly, ectoine is an inert drug with no effect on the epithelium functioning, and can provide local protective effect without toxic, chemical, and metabolic effects. Physico-chemical properties of the hydro-patch formed by ectoine and water molecules help the patch to stretch on the base of the ciliary apparatus of the respiratory epithelium as a "mucous blanket" without interfering with the mucous membrane protective function.

In international studies during the period of 2009–2011, the authors obtained data on the efficacy and safety of ectoine 2% nasal sprays and eye drops both in children and adults with allergic rhinitis in comparison with administration of cromoglicic acid, azelastine, beclomethasone [8]. In Russia the drug containing ectoine in a saline based nasal spray was registered for intranasal administration. The ability to generate hydro-patch by attracting water molecules to ectoine allows us to consider this medicine as a tool to protect the mucosal barrier.

The ***objective*** was to evaluate the efficacy of a nasal spray containing ectoine in the treatment of seasonal allergic rhinitis in children.

METHODS

STUDY DESIGN

An open randomized clinical trial was conducted.

ELIGIBILITY CRITERIA

Inclusion criteria: patients aged between 3 and 17 years diagnosed with seasonal allergic rhinitis (with severity score of rhinitis equal to or more than 2 points) and with sensitization to tree pollens with early spring dusting (birch, alder and/or hazel). All children in the period of exacerbations were administered antihistamines.

Non-inclusion criteria: planned administration of intranasal corticosteroids for a month prior to the study.

Exclusion criteria: administration of intranasal corticosteroids during the study period; conjunctivitis symptoms during the follow-up period; the appearance of signs of acute respiratory infection.

CONDITIONS

Four pediatric allergologists who work at municipal clinics (Perm – 3, Berezniki, Perm Region – 1) provided the inclusion of patients in the study.

RANDOMIZATION PROCEDURE

Researchers from each of the four centers received a random set of sealed envelopes. The number of envelopes in each set was equal to the planned number of patients: 22, 18, 14, and 9. An envelope included data on the only one variant of treatment ("antihistamine and saline solution with ectoine" or "only antihistamine") in a ratio of 1.5:1.

At the study onset, a patient or his legal representative (parent for a child under 14 years old) received a self-observation list that included the subjective assessment scale (see Section "Methods for outcome registration"). The patient (parent) had to conduct the daily assessment of rhinitis symptoms. If the symptom severity index reached 2 points, the patient (parent) was recommended to contact the doctor. The doctor opened the envelope and the information therein defined the treatment option.

DURATION OF THE STUDY

The run-in period started on April 1, 2015; after randomization, the follow-up period lasted for 21 days; the end of the study was planned not later than May 31, 2015. The randomization procedure and the beginning of the comparative study period were conducted from April 10 to May 11, 2015. Selection of the study period was associated with the expected exacerbation of the early spring pollenosis [9].

DESCRIPTION OF THE MEDICAL INTERVENTION

All children received oral age-recommended non-sedating antihistamines daily, for a period of exacerbation. After randomization, patients of the experimental group were additionally administered ectoine 2% nasal spray Aqua Maris Sens (JSC "Jadran" (JGL) Galenski Laboratories, Croatia) 3 or 4 times per day for a period of 21 days. The sponsor of the study provided the patients with the required spray at no cost.

STUDY OUTCOMES

We consider the following surrogate endpoints:

- the dynamics of the symptom severity on the 1^{st}, 10^{th}, and 21^{st} day of treatment (after randomization);
- necessity for additional therapy of rhinitis;
- termination of the study due to the intolerance to drugs or dissatisfaction with the treatment effect.

METHODS FOR OUTCOME REGISTRATION

Patients (or parents for children under 14 years old) assessed daily the symptom load severity (nasal congestion, itching, sneezing, rhinorrhea) according to the following scale:

- 0 - no symptoms;
- 1 - mild;
- 2 - moderate;
- 3 - severe.

The range of possible values ranged from 0 to 12 points. The same way the severity of non-nasal symptoms (cough, ocular symptoms) was evaluated. Data was recorded in the patient's diary.

Medicine record form included data on all medications the patients received daily: both prescribed by a doctor and occasionally applied to reduce acute symptoms.

A doctor visited patients or called them at least once in 10 days, supervised the proper and regular filling-in of the self-observation lists and medicine record forms, registered the acute symptoms of the disease or the adverse events that occurred.

ETHICAL REVIEW

Each patient or his legal representative provided the informed consent for observation; patients randomized to the experimental group signed the additional consent for application of an ectoine nasal spray. The study protocol (№ 3 dated March 25, 2015) has been approved by the Local Ethical Committee of the Perm State Medical University n.a. acad. E.A. Wagner.

STATISTICAL ANALYSIS

The sample size was not estimated previously.

Statistical analysis was performed using the package of statistical functions of "Microsoft Excel" program (Microsoft Office 2010). Quantitative data was described as means ± SDs, the significance of the differences between the two compared groups was evaluated using Student's t-test for unrelated samples. Qualitative characteristics were shown as percentages (%), the difference between the two proportions was assessed by z-test. The null hypothesis was rejected when $P<0.05$.

RESULTS

STUDY PARTICIPANTS

63 children were screened and 50 were enrolled into the study. Subjects were randomized in control group (n=20) and experimental group (n=30). Four patients discontinued the study, two cases both in experimental and control group. Two patients were excluded on the basis of the relevant exclusion criteria (one patient experienced acute respiratory infection on the day 8 of the study; the second one exhibited signs of conjunctivitis on the day 16 of the observation). The other two patients dropped out spontaneously (one patient moved to another region, the second one left without explanation when collecting the self-observation diaries). The data acquired from those patients was excluded from the analysis due to the incorrect treatment option: children with signs of severe exacerbation (according to the evaluation of symptom severity – more than 8 points out of 12 for a total of four rhinitis symptoms) had not been administered with a glucocorticoid. The total number of subjects enrolled in the analysis was 42 (experimental group: n = 24, control group: n = 18).

Subject characteristics of both experimental and control groups are presented in Table 1. The groups were comparable in age, prevalence of the primary clinical signs of the disease, severity of rhinitis symptoms. Total IgE concentration in children was similar.

Table 1. Subject characteristics at the moment of randomization procedure

Signs	Groups		*p*
	Primary (*n* =24)	Control (*n* =18)	
Age, months	128±48	128±39	0.980

Clinical manifestations of polinosis (%): ◊ allergic rhinitis; ◊ allergic conjunctivitis; ◊ bronchial asthma	 24 (100) 19 (79) 0	 18 (100) 15 (83) 1 (6)	 – 0.944 0.817
Rhinitis symptom load, points	4.6±2.1	3.8±1,9	0.150
Total IgE, IU/ml	413±391	459±314	0.724

PRIMARY RESULTS

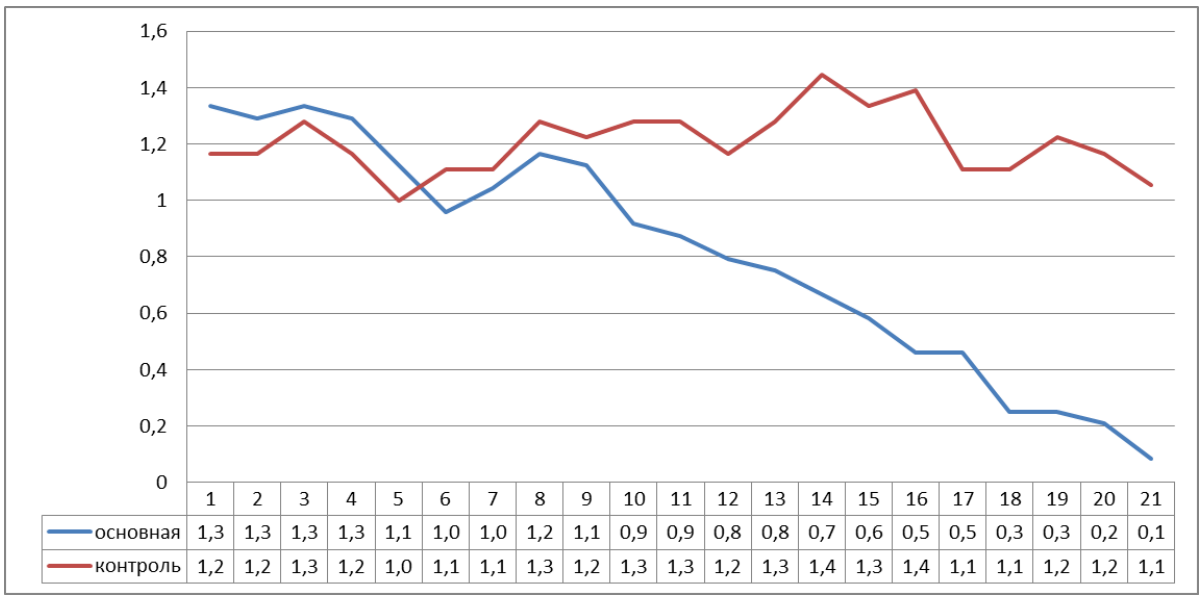
CLINICAL DATA DYNAMICS

Analysis of rhinitis symptoms showed that on the day 10 of the study the results were comparable in both groups. On the day 21, however, significant alterations in dynamics were registered in the experimental group patients receiving saline based ectoine solution (Table 2). We recorded the statistically significant differences between the experimental and control groups in the severity of nasal congestion starting on the day 14 (P = 0.01), rhinorrhea — day 15 (P = 0.036), itchy nose and sneezing — day 17 (P = 0.02; Figs. 1–4).

Table 2. Clinical assessment of the dynamics of incidence of rhinitis symptoms in children with seasonable allergic rhinitis (points)

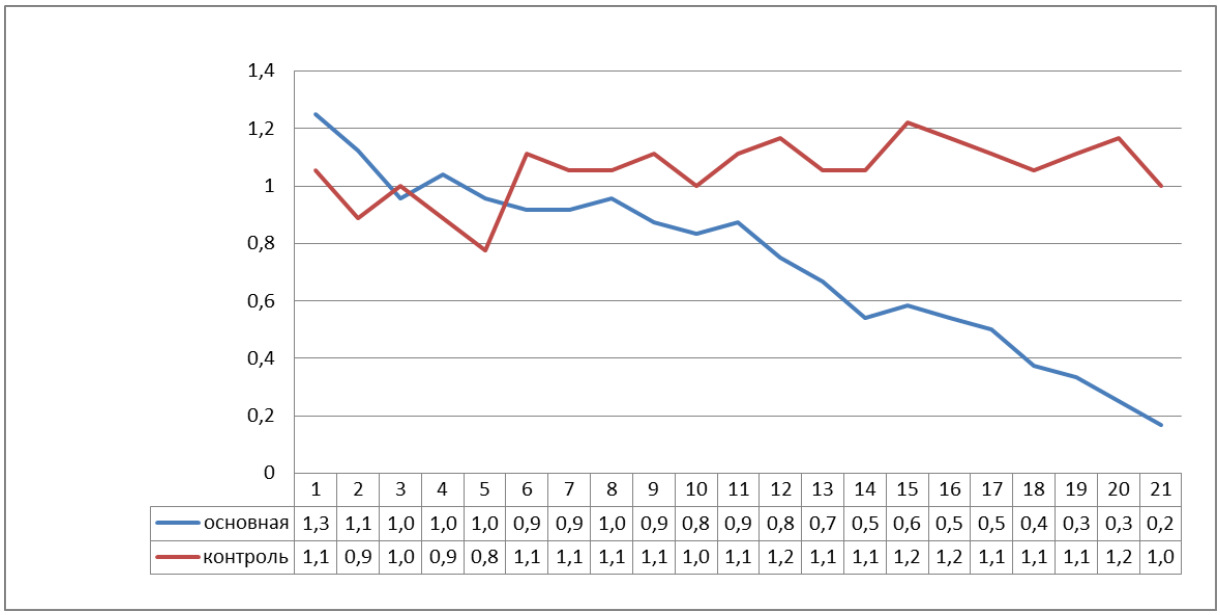
Symptoms	Experimental group (*n* =24)			Control group (*n* =18)			*P*		
	Days of treatment								
	1	10	21	1	10	21	1	10	21
Nasal congestion	1.3±0.9	0.9±0.8	0.1±0.3	1.2±0.6	1.3±1.1	1.1±0.9	0.486	0.261	0.001
Rhinorrhea	1.3±0.7	0.8±0.8	0.20±0.4	1.1±0.9	1.0±1.1	1.0±1.2	0.438	0.582	0.001
Itchy nose	0.8±0.8	0.5±0.7	0±0.2	0.7±0.8	0.7±1.0	0.6±0.9	0.790	0.426	0.022
Sneezing	1.2±0.8	0.7±0.8	0.1±0.3	0.9±0.5	0.9±1.1	0.8±0.9	0.124	0.462	0.003
Total	4.6±0.2	2.9±0.2	0.4±0.1	3.9±0.2	3.9±0.3	3.5±0.2	0.324	0.123	0.003

Fig. 1. Dynamics of the severity of nasal congestion in children with seasonal allergic rhinitis.



Note. *Experimental group values are in blue; control group values – in red.*

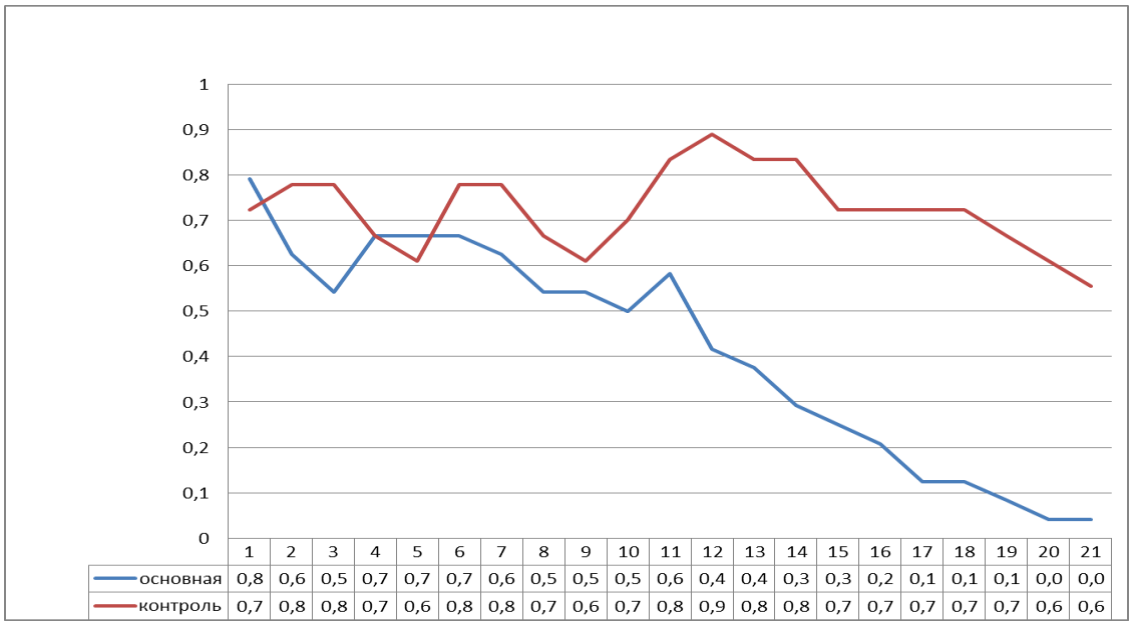
Fig. 2. Dynamics of the severity of rhinorrhea in children with seasonal allergic rhinitis.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
основная	1,3	1,1	1,0	1,0	1,0	0,9	0,9	1,0	0,9	0,8	0,9	0,8	0,7	0,5	0,6	0,5	0,5	0,4	0,3	0,3	0,2
контроль	1,1	0,9	1,0	0,9	0,8	1,1	1,1	1,1	1,1	1,0	1,1	1,2	1,1	1,1	1,2	1,2	1,1	1,1	1,1	1,2	1,0

Note. *Experimental group values are in blue; control group values – in red.*

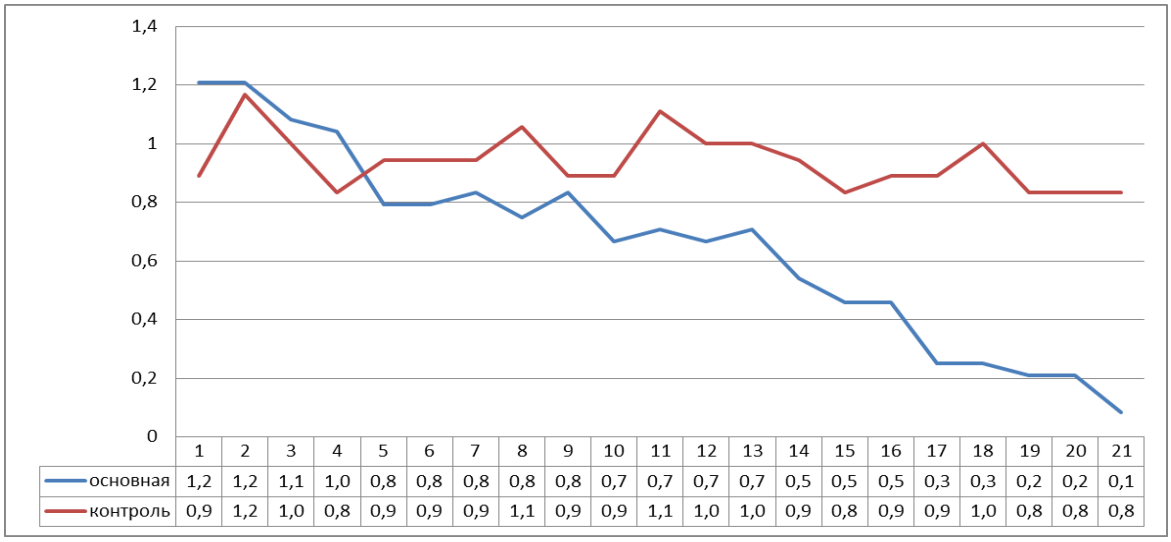
Fig. 3. Dynamics of the severity of itchynose in children with seasonal allergic rhinitis.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
основная	0,8	0,6	0,5	0,7	0,7	0,7	0,6	0,5	0,5	0,5	0,6	0,4	0,4	0,3	0,3	0,2	0,1	0,1	0,1	0,0	0,0
контроль	0,7	0,8	0,8	0,7	0,6	0,8	0,8	0,7	0,6	0,7	0,8	0,9	0,8	0,8	0,7	0,7	0,7	0,7	0,7	0,6	0,6

Note. *Experimental group values are in blue; control group values – in red.*

Fig. 4. Dynamics of the severity of sneezing in children with seasonal allergic rhinitis.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
основная	1,2	1,2	1,1	1,0	0,8	0,8	0,8	0,8	0,8	0,7	0,7	0,7	0,7	0,5	0,5	0,5	0,3	0,3	0,2	0,2	0,1
контроль	0,9	1,2	1,0	0,8	0,9	0,9	0,9	1,1	0,9	0,9	1,1	1,0	1,0	0,9	0,8	0,9	0,9	1,0	0,8	0,8	0,8

Note. *Experimental group values are in blue; control group values – in red.*

ADDITIONAL RESULTS

Analyzing the dynamics of the severity of concomitant allergic conjunctivitis, it was found that 2 out of the 4 symptoms had a significant positive dynamics in the experimental group. Itchy eyes symptom on the day 18 of treatment was assessed in both experimental and control groups [0.08 ± 0.28 points vs. 0.67 ± 0.97 points respectively; (P = 0.007)]; on the day 21 of therapy the severity rate of that symptom significantly was abrogated in experimental group [0 vs. 0.44 ± 0.7 respectively; (P = 0.016)].

Intensity of conjunctival hyperemia at a baseline was significantly higher in the experimental group than in control: 0.95 ± 0.8 and 0.5 ± 0.51 points respectively; (P = 0,043). On the day 10 the symptom severity between the two groups was similar (P = 0.960). Starting from the day 19, the rate was significantly lower in experimental group than in control: 0.04 ± 0.2 and 0.5 ± 0.86 respectively; (P = 0.015). The significant difference in the intensity of conjunctival hyperemia persisted on the day 21: 0 and 0.33 ± 0.6 respectively; (P = 0.030).

On the day 1 the watery eyes severity scores were higher in the experimental group than in control: 0.42 ± 0.77 and 0.05 ± 0.24 respectively, (P = 0.057); since the day 10 the difference between the groups dissapeared (for all checkpoints P> 0.05). That symptom disappeared entirely a day earlier in the experimental group than in the control group.

No significant differences were observed when compared the symptom severity scores of eyelid swelling and conjunctivitis (total assessment).

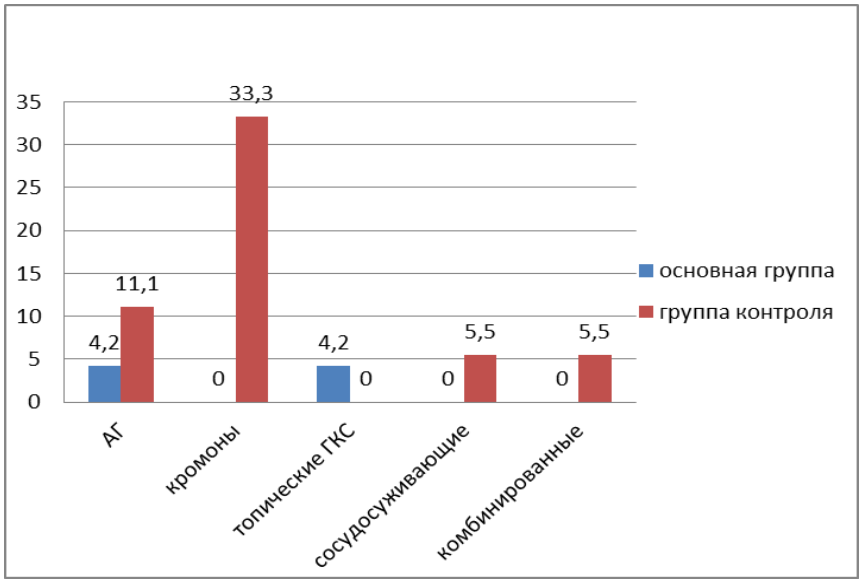
During the study period the cough was observed in 9 (38%) subjects of the experimental group and in 6 (33%) patients of the control group. Mean duration of the symptom was 4±6 and 3±5 days respectively. One (4%) patient of the experimental group complained of mild dyspnea for two days. The cough and shortness of breath disappeared without additional drug administration.

EVALUATION OF DRUG LOAD

According to the Protocol, all the subjects who participated in the study were administered antihistamines. Oral non-sedating antihistamines (desloratadine, cetirizine, loratadine) at an age-specific dosage for each drug were used for preseason-seasonal pattern (beginning 2-4 weeks before the expected continuation and exacerbation of reception throughout the period of exacerbation) or only during the acute season (beginning with the appearance of the first symptoms and regular intake during the acute period).

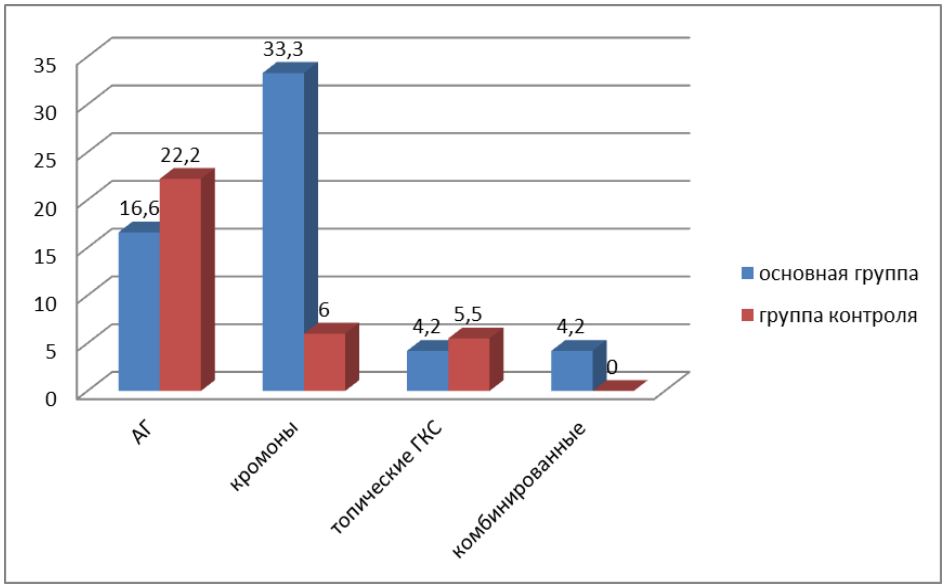
During the entire study period (21 days), 2 patients (8%) of the experimental group and 10 (56%) of the control group reported episodic self-administration of drugs for relief of rhinitis symptoms (P = 0.002). In all cases, patients applied the topical intranasal medications (Fig. 5). 14 patients (58%) of the experimental group and 8 patients (44%) of the control reported self-administration of topical medications for episodic treatment of allergic conjunctivitis (P = 0.557; See Fig. 6).

Fig. 5. Additional therapy in patients with seasonal allergic rhinitis.



Note for Figs. 5–6. *Experimental group values are in blue; control group values – in red. АГ – antihistamines; кромоны – cromons; топические ГКС – topical corticosteroids; сосудосуживающие – vasoconstrictor; комбинированные – combined.*

Fig. 6. Additional conjunctivitis therapy in patients with seasonal allergic rhinitis.



ADVERSE EVENTS

No adverse reactions in patients, medication rejection or elimination of the study due to the intolerance to drugs or dissatisfaction with the treatment effect were registered in the course of the clinical trial.

DISCUSSION

It is known that birch pollen count of 20 pollen grains per cubic meter (grains/ m^3) can provoke the development of clinical signs of the disease in some highly sensitive people. When pollen level increased up to 75 grains/m^3, symptoms may occur in the majority of patients sensitized to that allergen [10]. According to the results of conducted studies, in the Perm Region the first early spring trees pollen was registered in April and May. The maximum daily birch pollen count may exceed 3500 grains/m^3 [10]. The main mechanism for effect implementation of ectoine salt-based spray is the elimination of allergens or prevention of allergen contact with the mucosa due to the hydro-barrier effect. However, the control of symptoms or stable positive dynamics depends on the duration of the period of pollination (natural pollen allergen exposure). In the region of the study (the Urals, Central Russia) birch is the main provoker of plant pollen induced allergy. Its pollination period lasts for 26–45 days starting from the last decade of April and finishing at the first decade of June [10]. The main study period encompassed the peak period within the pollen count season. Therefore, the persistence of symptom control and stable positive dynamics on the days 14–19 of the study is expected and confirms the necessity of the barrier therapy (e.g., saline-based ectoine spray) throughout the peak period of pollination, for at least 3–6 weeks (required by a specificity of the study region and the type of polinosis).

In our opinion, a decrease in the severity symptoms scores of allergic rhinitis comparable to the results of positive dynamics of ocular symptoms scores (itching and redness of the conjunctiva) in the course of treatment are not associated with the direct effect of intranasal ectoine spray but with the mediated effect of reducing the intensity of the inflammatory process in the anatomically close area to the nasal mucosa [11]. These effects are described in other studies and may have clinical relevance in the treatment of patients as allergic rhinitis is frequently associated to allergic conjunctivitis.

STUDY LIMITATIONS

The main limitation is the lack of the data on the objectification of the results obtained by means of instrumental techniques (e.g., rhinomanometry for nasal congestion). In addition, more strict control of episodic therapy is required. Patients sometimes apply non-symptomatic medicines (cromolyn) in self-administration.

CONCLUSION

The obtained results indicate that the application of an ectoine nasal spray in combination with antihistamines for treatment of seasonal allergic rhinitis reduces core symptoms of the disease and requirement for episodic therapy, if compared to the antihistamine monotherapy.

Conflict of interest

The study was sponsored by JSC "Jadran" (JGL).

N.V. Minaeva has reported that she received honorarium for lectures from the company "Jadran" (JGL).

D.M. Shiryaeva has confirmed she has no financial support / conflict of interest to report.

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