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Sinupret® as add-on therapy to saline irrigation for children with acute Post-Viral Rhinosinusitis

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Abstract

Background: The present randomized controlled study investigated the efficacy of the complex herbal medicine Sinupret® syrup in the treatment of acute post-viral rhinosinusitis in children.

Methods: The patients were children aged from 6 to 11 years (mean 9.4 years old).
They were randomized into two groups. Both groups received a standard treatment including a symptomatic therapy and a saline therapy. Isotonic sea salt solution was given four times daily for a period of 14 days.
The treatment group received an additional treatment with Sinupret® syrup 3-times daily.
Using a 5-point scale (0–4 points), the physician evaluated the following symptomatic parameters at four successive visits (days 0, 5, 10 and 14): nasal congestion, nasal discharge, post-nasal drip and headache. Presence of cough in each group was recorded separately. Also using a 5-point scale (0–4 points), each patient gave a daily self-assessment of the following parameters from day 1 to day 10: rhinorrhea, headache, facial pain.

Results: Relative to symptomatic therapy + saline irrigation, significant improvements were found in seven of the eightsymptomatic parameters under complex treatment including Sinupret® syrup. The differences in facial pain and the incidence of cough in groups were not significant. The need for prescription of antibiotics in the treatment group was 28.5% less than in the control group. No adverse reactions to the herbal medicine occurred during the study period.

Conclusion: The complex herbal medicine Sinupret® syrup alleviates effectively the symptoms of acute post-viral rhinosinusitis in children. Furthermore, the prescription of antibiotics was also reduced.

Keywords: Rhinosinusitis, Herbal medicine, Sinupret syrup, Rhinorrhoea

Background

Acute rhinosinusitis (ARS) is an inflammatory disease of the nose and paranasal sinuses. It is most commonly caused by viral infections, mainly rhino- or adenoviruses [1].

ARS is a self-limiting disease lasting 7–14 days. In Ukraine approximately 54% of patients with ARS show a self-healing within this period. 46% of ARS patients suffer from prolonged symptoms or complications.

ARS comprises of viral ARS (common cold) and post-viral ARS. In the EPOS 2007 the term non-viral ARS was chosen to indicate that most cases of ARS are not bacterial. However this term led to confusion and in the EPOS 2012 guidelines the term post-viral ARS expressedthe same phenomenon. A small percentage of the patients with post-viral ARS can have bacterial ARS [2]. Acute post-viral rhinosinusitis is defined as an increase of symptoms after 5 days or persistence of symptoms after 10 days with less than 12 weeks duration.

Post-viral ARS is a common condition in the community, usually following viral Upper Respiratory Tract Infections. Post-viral ARS should not be diagnosed in patients with symptoms for less than 10 days unless a marked worsening of symptoms occurs after 5 days, and features of severe pain and a pyrexia of >38 °C are present. Symptoms occurring for longer than 12 weeks indicate the presence of chronic rhinosinusitis.

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According to the "European position paper on rhinosinusitis and nasal polyps" (EPOS), drug treatments for alleviating symptoms in post-viral ARS include topical corticosteroids, herbal medicine and aspirin. Therapeutic irrigation with isotonic saline is also used to reduce intranasal pressure.

While diagnosis of viral ARS is very frequent, with about 6.3 million diagnoses per year only in Germany [3], the number of post-viral ARS patients is not exactly known. Nonetheless, the post-viral ARS is of great socio-economic importance. It leads to major direct therapy costs and important indirect costs caused by loss of productivity and more days of absence from work in comparison to viral ARS [2].

Only about 0.5% of cases of ARS can be characterized as acute bacterial rhinosinusitis (ABRS). Typical symptoms of ABRS include purulent nasal discharge, tooth pain, facial pain, and unilateral tenderness to palpation in the projection of the maxillary sinus, worsening of symptoms after initial improvement, hyperthermia and neutrocytosis.

However, acute rhinosinusitis is the fifth most frequent diagnosis for the prescription of antibiotics, even though there is no proof that this shortens the duration of the illness. The frequent and unnecessary treatment with antibiotics has led to the development of increased resistance and, for this reason, alternative evidence-based treatment strategies are urgently necessary. One possible approach is to use herbal medicines [4–6].

The potential role of herbal therapy is particularly great in the treatment of post- viral ARS. As there is no evidence that infectious factors play a role in the aetiology of post-viral ARS, it is appropriate to employ symptomatic or pathogenetic treatment, rather than to use antivirals and antibiotics.

It is commonly known that the pathogenesis of post-viral ARS lies in the development of inflammation and related mucosal oedema, primarily in the osteomeatal complex (OMC). The function of the mucociliary transport system (MTS) is impaired against the background of the growing frontal ostium and sinus dysfunction and increased production of pathologically altered mucus. These changes result in progressive deterioration in OMC function, particularly in the ventilation and drainage of the paranasal sinuses.

Unsuccessful attempts have been made to treat post-viral ARS with several conventional agents, including decongestants, antibiotics, antiseptics, antihistamines, homeopathic products and secretolytics. Thus, treatment of post-viral ARS remains a topical problem.

One promising approach is to use a preparation which is capable of inhibiting a variety of pathological processes. One of these preparations is the complex herbal medicine Sinupret which is based on gentian, evening primrose, elder, verbena and sorrel. This herbal medicine has been shown to enhance ciliary activity in vitro [7] and to have anti-inflammatory activity in animal experiments [8]. It has a wide spectrum of pharmacological properties, including secretolytic, secretomotoric, antiviral, anti-inflammatory, and immunomodulatory effects. Jund et al. [9] performed a double blind randomized placebo-controlled study on 386 adult patients with acute viral rhinosinusitis. The active treatment group was given a daily dose for 15 days of 3 × 160 mg herbal medicine. The active treatment group showed more significant improvements in the sino-nasal outcome test, including the total score, the nasal symptoms, the rhinogenic symptoms and general quality of life.

Until now, no GCP-compliant analysis of Sinupret syrup has been carried out in the treatment of post-viral ARS in children of school-age (6–11 years).

We now report a similar study to Jund et al. on children aged 6–11 years, employing a syrup formulation of the herbal medicine.

Methods

Study design

The study was a prospective multicentre non-interventional randomized study on the treatment of post-viral ARS in children aged 6 to 11 years. The study compared a treatment with a complex herbal medicine - Sinupret® syrup - and standard treatment, as summarized in Table 1.

Sinupret is a phytopharmaceutical widely utilized for a variety of respiratory ailments including rhinosinusitis and bronchitis. The compound is a mixture derived from parts of five plants: gentian root (Radic Gentianae); primrose flowers with calyx (Flores Primulae cum Calibus), European vervain herb (Nebra Verbenae), sorrel grass (Herba Rumicis); Flowers of elderberry (Flores

Table 1 Study Treatments over 14 days

Groups	Pharmaceutical drug	Dosage	Duration
Treatment	• Therapeutic irrigation (isotonic sea salt solution)	4 times daily	14 days
	• Phytopreparation, syrup (Sinupret)	(3.5 ml), 3 times daily	
	• Symptomatic medications (episodically): paracetamol, nasal decongestants	Age-specific dosage	
Control	• Therapeutic irrigation (isotonic sea salt solution)	4 times daily	14 days
	• Symptomatic medications (episodically): paracetamol, nasal decongestants	Age-specific dosage	

Sambuci) (1: 3: 3: 3: 3). Table 1: Study Treatments over 14 days

Both groups were given symptomatic medication (paracetamol or nasal decongestants if necessary and both were treated with therapeutic irrigation with isotonic sodium chloride solution 4 times daily. The treatment group was given the herbal medicine – Sinupret syrup – 3 times daily at the age-specific dosage of 3.5 ml, additionally.

Study population

The study population consisted of 120 children, 64 boys and 56 girls, aged 6 to 11 years (mean 9.4 years old) and with acute post-viral rhinosinusitis. The treatment group contained 65 children and the control group 55.

The number of patients with prolonged symptom > 10 days and those which had severe symptoms after 5 days is shown in Table 2.

Inclusion criteria

The principle inclusion criteria was acute post-viral rhinosinusitis, with persistence of acute symptoms for 10 days or exacerbation of symptoms after day 5.

The following ***five key symptoms*** were rated by the physician with 0–4 points on the major sinusitis severity score (MSS score): nasal discharge, nasal congestion, post-nasal drip, headache, facial pain, with a total score of up to 15 points (of the maximum possible sum 20 points). The scale of the scores is as follows: 0 absent, 1 slight, 2 moderate, 3 severe, 4 very severe.

Exclusion criteria

- Administration of the herbal preparation within 30 days prior to the episode of rhinosinusitis
- Diagnosis of allergic rhinosinusitis
- Known intolerance to primrose drugs
- Severe acute disease requiring hospitalization or treatment with antibiotics
- Immune deficiency
- Chronic pathology and anatomical anomalies of the osteomeatal complex, which may influence the outcome of the disease

Table 2 Number of the patients with prolonged symptom > 10 days and those which had severe symptoms after 5 days

Groups	Patients with prolonged symptoms > 10 days		Patients with severe symptoms after 5 days	
	Number of patients	%	Number of patients	%
All patients $n = 120$	101	84.2%	19	15.8%
Treatment group $n = 65$	54	83.2%	11	16.8%
Control group $n = 55$	47	85.4%	7	12.6%

Withdrawal criteria

- Indications for antibiotic therapy
- Adverse reactions to the study drug
- Protocol violation

Research methodology

During the study period four visits were conducted: visit 1 (day 0), visit 2 (day 5), visit 3 (day 10) and visit 4 (day 14). Symptoms were assessed by the physician and the patients. The five key symptoms were assessed by the physician at each visit. In addition, the key complaints of rhinorrhea, headache, facial pain, were assessed by the patients on a 0–4 point scale daily. Presence of cough was recorded separately.

Efficacy criteria

The primary criteria were the improvements in symptoms. The secondary criteria was the frequency of transition to prescription of antibiotics to assess the transition from post-viral ARS to acute bacterial rhinosinusitis (ABRS).

Data analysis

The data were presented descriptively. Differences between the two groups were tested with the paired test, using a two-sided 95% Confidence-Intervall (95% CI) with the significance $p \leq 0.05$.

Results

Study population

All the 120 patients completed the study period of 14 days.

Five (5) patients in the treatment group and nine patients in the control group were excluded from the study for reasons of protocol violation and data of these patients were excluded from analysis. These patients were offset by recruitment of additional patients.

Antibiotics therapy

Five (5/65) of the patients (7.7%) in the treatment group had to be treated with antibiotics, in comparison to six (6/55) patients (10.9%) in the control group. This difference was not statistically significant ($p > 0.05$). In most cases (9 patients), treatment with antibiotics was started at visit 3 due to repeated increase in the temperature (39 °C and higher), re-worsening severity of sinusitis symptoms.

Symptoms assessed by the physician

Figure 1 shows the physician's assessment of the nasal congestion symptom at visit 1 to 4. Both groups showed comparable symptoms at visit 1 (v1). At visit 2 (v2), nasal congestion was significantly less in the treatment group than in the control group ($p = 0.041$). From visit 3 (v3) to visit 4 (v4) nasal congestion of both groups showed further reduced symptoms to zero at visit 4.

Figure 2 shows the physician's assessment of the nasal discharge symptom at visits 1 to 4. The differences at v2 and v3 are statistically significant ($p < 0.038$).

The physician's assessment of post-nasal drip was also significantly lower in the treatment than in the control group at v2 (1.33 vs. 0.83, $p = 0.044$).

The physician's headache assessment also showed that this symptom was lower in the treatment group compared to the control one at v2. (0.45 vs. 0.32, $p = 0.048$).

There was a trend to less facial pain in the treatment group at v2, but the differences were not statistically significant (0.27 vs. 0.42, $p = 0.1$).

Furthermore, cough was observed in 60.8% of the patients of the treatment group and in 59.7% of the patients from the control. At the time of the visit 2 (Day 5) cough was recorded in 37.4% of the patients of the treatment group and in 43.2% of the patients from the control but these were not statistically significant.

Symptoms assessed by the patients

Figure 3 shows the patient's self-assessment of rhinorrhea for the first 10 days of treatment. At the beginning of the study (day 1 and day 2) the rating of the patients in both groups was comparable. Significantly less rhinorrhea was found in the treatment group on days 3, 4, 5, 6 and 7 (all $p < 0.05$). Similar results were obtained for self-assessed headache and facial pain.

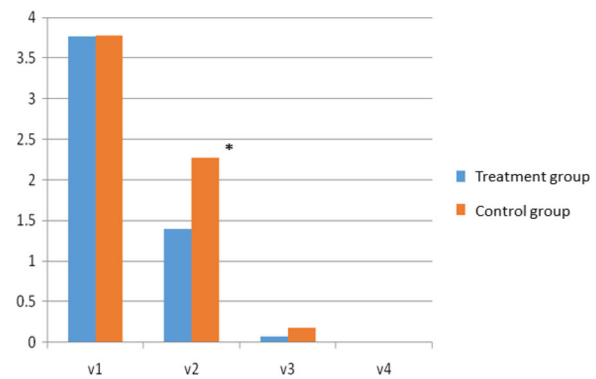

Fig. 1 Physician's assessment of the nasal congestion symptom at visit 1 to visit 4

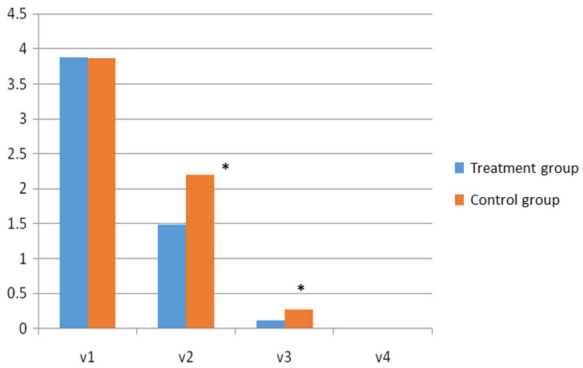

Fig. 2 Physician's assessment of the nasal discharge symptom at visit 1 to visit 4. The differences at v2 and v3 are statistically significant ($p < 0.05$)

Discussion

Acute post-viral rhinosinusitis is a very common and economically important condition, involving inflammation of the nasal mucous membranes and paranasal sinuses [2, 3]. The principle symptoms are inflammation and mucosal oedema, primarily in the osteomeatal complex. The function of the mucociliary transport system is impaired against the background of increased production of pathologically altered mucus. These symptoms develop after the acute viral infection and can be considered as the next stage of development of the disease after acute viral sinusitis when the symptoms persist for more than 10 days. Antiviral treatment is ineffective. Saline irrigation proved efficient for improving the symptoms in randomized, placebo-controlled studies [10]. International and Ukrainian guidelines consider irrigation therapy as a relevant treatment to enable a better secret mobilization for all the forms of ARS. Because of these benefits, we used irrigation therapy in both groups as a component of the basic therapy with local activity. If there would be an impact of irrigation therapy, the impact

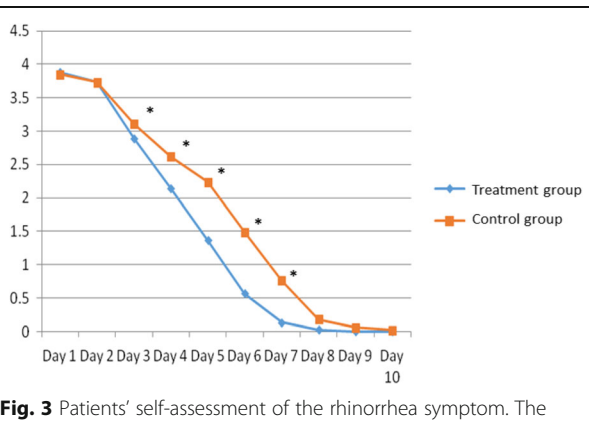

Fig. 3 Patients' self-assessment of the rhinorrhea symptom. The differences between the groups are statistically significant from day 3 to day 7 ($p < 0.05$)

can be assumed as similar in both groups, since the group parameters are comparable. Evaluated differences in severity of symptoms between the treatment groups can therefore be assumed to be related to the herbal medicine. An additional herbal medicine with multiple systematic activities could be useful in alleviating the symptoms of acute post- viral rhinosinusitis and might inhibit the transition to a bacterial infection. There is an extensive evidence from in vitro and animal studies that the complex herbal medicine Sinupret possesses a variety of such relevant activities.

Rossi et al. [8] investigated the effects of Sinupret in an in vivo model of acute inflammation, carrageenan-induced pleurisy in rats. Sinupret significantly reduced exudate volume and leukocyte numbers in the pleural exudate. There were also parallel reductions in the expression of the enzyme cyclooxygenase-2, which forms pro-inflammatory prostaglandin E_2. Zhang et al. [7] showed that Sinupret promotes transepithelial chloride transport, and enhances ciliary beat frequency and airway surface liquid depth. Taken together, these activities would tend to enhance mucus clearance. In vitro studies suggest that one underlying mechanism may be the binding of antioxidant components of the herbal medicine to CFTR (cystic fibrosis transmembrane conductance regulator), resulting in direct activation and enhanced chloride transport [11].

The present randomized controlled study investigated the efficacy of Sinupret in alleviating the symptoms of acute post-viral rhinosinusitis in children aged 6 to 11 years. Relative to standard treatment, significant improvements were found in the treatment group in five key symptoms as assessed by the physician and in three key symptoms as assessed by the patient. There was also a reduction in the number of patients given antibiotic treatment. Similar findings have been made in a study with adult patients [9].

During the study period none of the patients showed any adverse reactions to Sinupret. That supports the safety of the treatment in children.

Limitations

This was a randomized non-interventional study. Limitations include the lack of virological information and the lack of radiological measurements.

Conclusion

Sinupret is an effective treatment for the symptoms of acute post-viral rhinosinusitis in children. Sinupret could also encourage reduction in the unnecessary prescription of antibiotics for this condition. This is important in the light of the development of bacterial resistance.

Abbreviations

ABRS: Acute bacterial rhinosinusitis; CFTR: Cystic fibrosis transmembrane conductance regulator; MSS score: Major sinusitis severity score; v1, 2, 3, 4: visits 1, 2, 3, 4

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None.

Authors' contributions

VP: creation of the study design, protocol, data processing and interpretation. IK: work with patients, data collection. Both authors read and approved the final manuscript.

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Prof. Popovich is the Head of the Department of Otolaryngology at Ivano-Frankivsk University, Ukraine.
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Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Department of Otolaryngology, Ivano-Frankivsk National Medical University (protocol № 22 from the 23-th of October, 2015), Ukraine
Participants signed an informed consent form.

Declarations

The authors confirmed the absence of conflict of interests.

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