Efficacy and safety of combined treatment of acute rhinosinusitis by herbal medicinal product Sinupret and mometasone furoate nasal spray

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Abstract

Objective: Herbal medicinal products have a well-established role in therapy of upper airway inflammations. Current evidence supports the use of intranasal corticosteroids for improvement in clinical symptoms of uncomplicated acute rhinosinusitis (ARS). We aimed to evaluate efficacy and safety of combined therapy by mometasone furoate nasal spray (MFNS) and oral herbal medicinal product Sinupret in comparison to MFNS monotherapy when treating mild to moderate ARS.

Methods: Forty-six ARS patients were divided into two groups. Group 1 (n=23) received herbal drug Sinupret, 160 mg per os, three times daily and MFNS 200 μg twice daily for 7 days. Group 2 (n=23) received only MFNS 200 μg twice daily for 7 days. We assessed total symptom score (TSS), individual symptom scores for each symptom (nasal obstruction, rhinorrhea, postnasal drip, facial pain/pressure, impaired sense of smell) and endoscopic findings (mucosal edema, mucopurulent secretion), before and after treatment.

Results: Significant improvement of all clinical parameters was found after both treatment modalities (p<0.000). We observed lower post-treatment TSS (p=0.002), nasal obstruction (p=0.001), rhinorrhea (p=0.001), facial pain (p=0.001), impaired sense of smell (p=0.002), mucosal edema (p=0.003) and mucopurulent secretion (p=0.001) in MFNS/Sinupret group than in MFNS group. We found no adverse events in MFNS/Sinupret group, while only 1 patient reported mild epistaxis and 1 patient reported dryness in the nose in MFNS Group.

Conclusion: Our results suggest better efficacy of combined MFNS/Sinupret therapy of ARS on nasal symptoms and endoscopic findings, with the absence of adverse events in comparison to MFNS monotherapy.

Keywords: Glucocorticoids, inflammation, medicinal plants, rhinitis, sinusitis.

Özet: Akut rinosinüzit tedavisinde bitkisel tibbi ürün Sinupret ile mometazon furoatın kombine kullanımı etkinliği ve güvenilirliği


Yöntem: Kırk altı akut rinosinüzitli hastanın iki gruba ayrıldı. Grup 1 (n=23) 160 mg, 3 kez gün, Sinupret, 3 kez gün, mometazon furoate spray 200 μg kullanıldı. Grup 2 (n=23) ise sadece 7 gün süreyle 2 kez gün, mometazon furoate spray 200 μg kullanıldı.Tedavi öncesi ve sonrası semptomlar ayrı ayrı (nose obstruction, rhinorrhea, postnasal drip, facial pain/pressure, impaired sense of smell) ve endoskopik bulgular (mucosal edema, mucopurulent secretion) değerlendirildi.

Bulgular: Tedavi sonrası her iki gruptan da tüm klinik parametrelerde düzeltme gözlandı (p<0.000). MFNS/Sinupret grubunda MFNS grubundan daha düşük toplam semptom skoru (p=0.002) ve 2 kez gün, mometazon furoate spray 200 μg kullanıldı. Grup 2 ise sadece 7 gün süreyle 2 kez gün, mometazon furoate spray 200 μg kullanıldı. Çalışmada teda- vi öncesi ve sonrası semptomlar ayrı ayrı (nose obstruction, rhinorrhea, postnasal drip, facial pain/pressure, impaired sense of smell) ve endoskopik bulgular (mucosal edema, mucopurulent secretion) değerlendirildi.

Bulgular: Tedavi sonrası her iki grubunun klinik parametrelerde düşüş gözlandı (p<0.000). MFNS/Sinupret grubunda MFNS grubundan daha düşük toplam semptom skoru (p=0.002), burun tıkanıklığı (p=0.001), burun akıntısı (p=0.001), yüz ağrısı (p=0.001), koku bozukluğu (p=0.002), mukoza edemi (p=0.003) ve mukoaurül skresyonunun (p=0.001) düşmesi gözlandı. MFNS/Sinupret grubunda hiç bir yan etki görülmedi, sadece MFNS grubunda 1 hasta hafif epistaksis ve 1 burun kurutulması gözlandı.

Sonuç: Sonuçlarımız, akut rinosinüzit tedavisinde MFNS/Sinupret kombine tedavinin favorable etkilerini ve MFNS monoterapinin etkisini göstermiştir. MFNS/Sinupret kombine tedavisinin favorable etkilerini ve MFNS monoterapinin etkisini göstermiştir. MFNS/Sinupret kombine tedavisinin favorable etkilerini ve MFNS monoterapinin etkisini göstermiştir.

Anahtar sözcükler: Glukokortikoidler, inflamasyon, tibbi bitki, rinin, sinüzit.
Acute rhinosinusitis (ARS) is an inflammatory disease with a sudden onset including the mucosal membrane of paranasal sinuses and both nasal cavities. About 98 to 99.5% of the cases of ARS are caused by viruses, especially rhinoviruses, coronaviruses, parainfluenza, and influenza viruses, and adenoviruses. Secondary bacterial infection is observed in about 0.5 to 2% of cases. The pathophysiology of ARS is complex with a dominant role of inflammatory mucosal swelling, confining of natural sinus ostia in the area of ostiomeatal complex and sphenoethmoidal recess, and impaired mucociliary transport. Viral infections disturb the function of ciliated cells of the pseudostratified respiratory epithelium, leading to mucociliary clearance impairment. This results in increase of cytokine and chemokine production, neutrophil chemotraction, and bradykinin and leukotrienes releases. Therefore, vessel dilation leads to higher mucosal swelling. Transudation and mucosal gland secretion accumulation within the sinuses favor the development of bacteria which release toxins to develop inflammation, leading to a cruel circle effect.

Antibiotics are the most common treatment agents in ARS. However, as ARS is mostly a viral disease, the moderate benefits of antibiotics should be weighed against associated risks such as allergic reactions, gastrointestinal diseases and the development of resistant bacterial germs. There is a reasonable evidence of use of intranasal corticosteroids in the treatment of ARS. Meltzer et al. demonstrated the efficacy of mometasone furoate nasal spray as an effective monotherapy in uncomplicated ARS, maintaining a proposal to decrease recommending antibiotics for patients presenting with these clinical outcomes. The other authors suggest the use of steroid and a topical antibiotic combination into the nasal cavity healing uncomplicated bacterial ARS.

Herbal medicines have been used for centuries for the treatment of many disorders. However, to date there are only several controlled, randomized analyses which evaluated the effectiveness of herbal medicine in therapy of ARS. Sinupret is a trademarked herbal preparation developed in Germany, available in tablet and drop forms, and composed of five herbal extracts: gentian (Gentiana lutea, root); primrose (Primula veris, flower); common sorrel (Rumex acetosa, herb); elder (Sambucus nigra, flower); European vervain (Verbena officinalis, herb). Previous investigations clearly demonstrated mucolytic, secretomotoric, anti-inflammatory, antiviral and antibacterial effects of this medicinal product. These characteristics, as well as the results of two double-blind, placebo-controlled studies recommended the use of Sinupret as a good treatment option in both ARS and chronic rhinosinusitis (CRS). The aim of our study was to evaluate the efficacy and safety of combined mometasone furoate nasal spray (MFNS) and oral Sinupret therapy in comparison to MFNS monotherapy when treating mild to moderate ARS. To our knowledge, this is the first such study presented in the literature.

Materials and Methods

Study design

This was a non-interventional, non-placebo controlled, case-control study of two consecutive case series, based on the treatment of ARS. We conducted a retrospective analysis of prospectively collected data at three institutions from January to December 2016. This investigation was conducted in accordance with the Declaration of Helsinki. The local Ethics Committee approved the study protocol (MFVMA06/16-18/) and we obtained written informed consent from each patient.

Study participants

Forty-six (n=46) adult patients with diagnosis of ARS according to the criteria of the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2012), aged from 18 to 61 years were enrolled in the study. Patients had inflammation of the nasal cavity/paranasal sinuses for 7 or more days and less than 12 weeks with at least two of the following symptoms: nasal obstruction, anterior nasal secretion/postnasal drip, facial pain/pressure, and/or impaired or loss of the sense of smell. On nasal endoscopic examination, patients could have mucosal edema and mucopurulent secretion predominantly in the middle meatus.

The patients were divided into two groups. Group 1 (n=23) received herbal medicinal product Sinupret® forte tablets of 160 mg (Bionorica, Neumarkt, Germany), three times daily and MFNS (Nasonex®, Merck Sharp & Dohme, Hertfordshire, UK) 200 μg twice daily (two puffs in each nostril in the morning and in the evening) for 7 days. Group 2 (n=23) received only MFNS 200 μg twice daily for 7 days.

Exclusion criteria were: younger than 18 and older than 65 years, CRS with or without nasal polyps, nasal/paranasal sinus surgery within 6 months before study, nasal septum deviation and/or middle turbinate hypertrophy significantly impairing nasal airflow and corticosteroid spray application, systemic diseases affecting the nose (cystic fibrosis, Churg-Strauss syndrome, Wegener’s granulomatosis, etc.), seasonal allergic rhinitis, bronchial asthma, aspirin sensitivity, hypersensitivity to study medications, the use of oral or
topical antibiotics, antihistamines, corticosteroids and leukotriene antagonists within the four weeks before the start of the study, the use of mucolytics, decongestants and analgesics within the 7 days before the investigation, pregnancy and lactation, diabetes mellitus, and smoking. Subjects were excluded if they had symptoms or signs of severe bacterial ARS (fever >38°C, persistent severe unilateral facial or tooth pain, facial swelling, profuse unilateral mucus/secretion).

Clinical evaluation

Intensity of 5 rhinosinusitis symptoms (nasal obstruction, rhinorrhea, postnasal drip, facial pain/pressure, impaired sense of smell) was assessed at the start of the study (visit 1) and within the two days after the end of investigation (visit 2) using a visual analogue scale (VAS) (0–10 cm; from 0=absent to 10=maximum intensity). Patients indicating their symptoms’ score to be from 0 to 3 were diagnosed as “mild ARS”. Symptoms in the score range from 4 to 7 were diagnosed as “moderate ARS” while the score from 8 to 10 with fever of above 38°C for at least 3 days were diagnosed as “severe ARS”. The patients with severe disease were excluded from investigation.

At visits 1 and 2, a rhinologist with proven experience in nasal endoscopy used a 4 mm 0° endoscope to evaluate the presence of mucosal edema and mucopurulent secretion in the middle meatus. A four-point scales were used for assessment of endoscopic findings: mucosal edema scored from 0=no edema to 3=severe edema; mucopurulent secretion from 0=none to 3=profuse. The maximum endoscopic score is 6, bilaterally for each endoscopic sign. According to the EPOS 2012 recommendations, radiological examinations (X-ray, CT, and MRI) or bacteriological examination were not used in the diagnostics of ARS.[13]

During the investigation, patients recorded their symptom scores on diary cards twice daily, in the morning and in the evening, and the same specialist recorded scores at the visit 2.

The efficacy endpoints were mean total symptom score (TSS; sum of the scores for nasal obstruction, rhinorrhea, postnasal drip, facial pain/pressure, impaired sense of smell), individual symptom score (score for each nasal symptom) and endoscopic score for each sign (mucosal edema, mucopurulent secretion), at the visit 1 and visit 2.

Safety

Reported adverse events were recorded throughout the study, with severity grades as mild, moderate and severe. At visit 2, nasal examination, laboratory tests and vital signs assessment were performed. Therefore, the development of any medical complications associated with progression of rhinosinusitis (orbital, endocranial or bone complications) were also recorded during the study.

Statistical analysis

The parameters have been expressed as mean±standard deviation. For between-group comparison, a non-parametric Mann-Whitney U test was used. The paired comparisons within a group were performed using the Wilcoxon’s test. P values <0.05 were considered significant. The analysis was performed by using the SPSS software (Statistical Package for the Social Sciences, version 15.0; SPSS Inc., Chicago, IL, USA).

Results

Forty-six patients (26 men and 20 women), aged between 18 and 61 years (mean age 41.06±28.91) diagnosed with ARS were included in this investigation. All numerical data presenting the demographic characteristics, total symptom score, individual symptom scores and endoscopic findings (mucosal edema, mucopurulent secretion), before and after two different treatment modalities are presented in Table 1. Results concerning all parameters’ statistical significances before and after the MFNS and MFNS/Sinupret treatment are presented in Table 2.

At the visit 1, we found no significant difference regarding the TSS, nasal obstruction score, rhinorrhea score, postnasal drip score, facial pain/pressure score and loss of the sense of smell score (p>0.05 for all parameters) between two investigation groups. We also found no significant difference between the MFNS and MFNS/Sinupret group regarding the mucosal edema (p=0.003) and mucopurulent secretion (p=0.001) (Table 1).

After the treatment, we found highly significant decrease of all clinical parameters in both MFNS and MFNS/Sinupret groups (p<0.000 for all parameters) (Figs. 1–3).

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After the treatment, we found highly significant decrease of all clinical parameters in both MFNS and MFNS/Sinupret groups (p<0.000 for all parameters) (Figs. 1–3).

At the visit 2, we observed significantly lower levels of TSS (p=0.002), nasal obstruction score (p=0.001), rhinorrhea score (p=0.001), facial pain/pressure score (p=0.001), impaired sense of smell score (p=0.002), mucosal edema (p=0.003) and mucopurulent secretion (p=0.001) in MFNS/Sinupret group than in MFNS group. On the other hand, we found significantly lower postnasal drip score (p=0.018) in ARS patients receiving only MFNS in comparison to those receiving MFNS and Sinupret (Table 1).
The safety of two different treatment modalities was also evaluated. None of the patients of MFNS/Sinupret group reported any adverse events, and all their vital signs and laboratory tests were normal. Among the participants of MFNS group, 1 patient had mild epistaxis and 1 patient reported the sense of dryness in the nose. All patients in this group had normal vital signs and laboratory tests.

Discussion

Currently, nasal corticosteroid has turn out to be a conventional adjuvant therapy in the treatment of both ARS and CRS. Pharmacologically, novel nasal steroids [i.e. MFNS and fluticasone propionate (FPNS)] seem to have considerably advanced lipid solubilities and topical potencies, and reduced systemic bioavailabilities than old generation nasal steroids. Previous investigations with patients suffering from uncomplicated ARS suggest that MFNS can be better monotherapy option than antibiotic therapy. MFNS 200 μg twice daily monotherapy is well accepted and extensively stimulated excessive alleviation of utmost ARS symptoms compared with placebo and amoxicillin. The results of our study demonstrated that 7-days MFNS monotherapy improves all nasal symptoms and endoscopic findings in patients with uncomplicated form of ARS. However, we also showed that combined use of herbal drug Sinupret with MFNS improve the efficacy of ARS treatment regarding the almost all symptoms and local signs of acute sinonasal inflammation. The results suggest that addition of Sinupret to MFNS leads to better improvement of nasal obstruction, rhinorrhea, facial

Table 1. Demographic characteristics of study population and clinical parameters before and after therapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MFNS (n=23) mean±SD (range)</th>
<th>MFNS+Sinupret (n=23) mean±SD (range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>13/10</td>
<td>13/10</td>
<td>1.000</td>
</tr>
<tr>
<td>Age</td>
<td>42.70±2.43 (18–61)</td>
<td>40.39±2.60 (18–61)</td>
<td>0.524</td>
</tr>
<tr>
<td>Nasal obstruction (B)</td>
<td>6.48±0.14 (5–7)</td>
<td>6.13±0.21 (4–7)</td>
<td>0.299</td>
</tr>
<tr>
<td>Nasal obstruction (A)</td>
<td>3.00±0.15 (2–4)</td>
<td>2.09±0.06 (2–3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Rhinorrhea (B)</td>
<td>6.61±0.10 (6–7)</td>
<td>6.22±0.17 (5–7)</td>
<td>0.094</td>
</tr>
<tr>
<td>Rhinorrhea (A)</td>
<td>4.13±0.13 (3–5)</td>
<td>3.30±0.18 (2–5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Postnasal drip (B)</td>
<td>6.43±0.16 (4–7)</td>
<td>6.43±0.12 (5–7)</td>
<td>0.701</td>
</tr>
<tr>
<td>Postnasal drip (B)</td>
<td>2.87±0.10 (2–4)</td>
<td>3.30±0.15 (2–5)</td>
<td>0.018</td>
</tr>
<tr>
<td>Facial pain/pressure (B)</td>
<td>6.70±0.15 (4–7)</td>
<td>6.48±0.11 (6–7)</td>
<td>0.052</td>
</tr>
<tr>
<td>Facial pain/pressure (A)</td>
<td>2.96±0.13 (2–4)</td>
<td>1.91±0.11 (1–3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Impaired sense of smell (B)</td>
<td>6.35±0.12 (5–7)</td>
<td>6.13±0.17 (5–7)</td>
<td>0.402</td>
</tr>
<tr>
<td>Impaired sense of smell (A)</td>
<td>3.04±0.13 (2–4)</td>
<td>2.04±0.12 (1–3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total symptom score (B)</td>
<td>32.57±0.41 (29–35)</td>
<td>31.39±0.53 (26–34)</td>
<td>0.078</td>
</tr>
<tr>
<td>Total symptom score (A)</td>
<td>15.17±0.40 (12–19)</td>
<td>13.48±0.25 (12–16)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mucosal edema (B)</td>
<td>5.61±0.10 (5–6)</td>
<td>5.52±0.12 (4–6)</td>
<td>0.682</td>
</tr>
<tr>
<td>Mucosal edema (A)</td>
<td>2.70±0.13 (1–4)</td>
<td>2.22±0.09 (2–3)</td>
<td>0.003</td>
</tr>
<tr>
<td>Mucopurulent secretion (B)</td>
<td>4.83±0.16 (4–6)</td>
<td>4.96±0.15 (4–6)</td>
<td>0.522</td>
</tr>
<tr>
<td>Mucopurulent secretion (A)</td>
<td>2.87±0.11 (2–4)</td>
<td>1.83±0.14 (1–3)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

A: after treatment, B: before treatment, MFNS: mometasone furoate nasal spray, SD: standard deviation

Table 2. Radiologic findings of patients with paranasal sinus fungus ball.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MFNS</th>
<th>MFNS+Sinupret</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal obstruction (B–A)</td>
<td>-3.46 (p&lt;0.000)</td>
<td>-4.05 (p&lt;0.000)</td>
</tr>
<tr>
<td>Rhinorrhea (B–A)</td>
<td>-2.09 (p&lt;0.000)</td>
<td>-3.30 (p&lt;0.000)</td>
</tr>
<tr>
<td>Postnasal drip (B–A)</td>
<td>-3.54 (p&lt;0.000)</td>
<td>-3.13 (p&lt;0.000)</td>
</tr>
<tr>
<td>Facial pain/pressure (B–A)</td>
<td>-3.74 (p&lt;0.000)</td>
<td>-4.57 (p&lt;0.000)</td>
</tr>
<tr>
<td>Impaired sense of smell (B–A)</td>
<td>-3.31 (p&lt;0.000)</td>
<td>-4.09 (p&lt;0.000)</td>
</tr>
<tr>
<td>Total symptom score (B–A)</td>
<td>-1.74 (p&lt;0.000)</td>
<td>-1.79 (p&lt;0.000)</td>
</tr>
<tr>
<td>Mucosal edema (B–A)</td>
<td>-2.91 (p&lt;0.000)</td>
<td>-3.3 (p&lt;0.000)</td>
</tr>
<tr>
<td>Mucopurulent secretion (B–A)</td>
<td>-1.96 (p&lt;0.000)</td>
<td>-3.15 (p&lt;0.000)</td>
</tr>
</tbody>
</table>

B–A: before treatment-after treatment, MFNS: mometasone furoate nasal spray
pain/pressure and impaired sense of smell, as well as better resolution of mucosal edema and mucopurulent secretion from the nasal middle meatus. Therefore, TSS is significantly lower after the combined treatment in comparison to MFNS monotherapy.

Sinupret has been developed using the extraction of the phytopharmaceuticals contained in five herbs: gentian (Gentiana lutea), primrose (Primula veris), common sorrel (Rumex acetosa), elder (Sambucus nigra), and European vervain (Verbena officinalis). The antiinflammatory action of Sinupret has been demonstrated in experimentally induced pleural inflammation in rats. The rats in which this herbal drug was administered orally one hour before treatment showed a lower volume of pleural effusion, less infiltration of polymorphonuclear leukocytes and decreased levels of prostaglandins in the exudates. This antiinflammatory effect can be attributed to the polysaccharides and tannins in sorrel and the iridoids in vervain.

Also, Sinupret has antiviral effect against adenoviruses, human rhinoviruses, respiratory syncytial virus, coxsackievirus, influenza and parainfluenza virus. The mechanism of this action is inhibition of neuraminidase, an important enzyme for process of viral replication. Sinupret has bactericidal effects on Gram-positive and Gram-negative bacteria, but this medication is not effective against Escherichia coli. These antiinflammatory and antimicrobial effects of Sinupret lead to a better reduction of nasal obstruction, rhinorrhea, facial pain and impaired sense of smell in patients on combined therapy. The better resolution of mucopurulent middle meatus discharge in our patients from MFNS/Sinupret group can be explained by antibacterial action of this herbal drug.

However, after the treatment (visit 2), our patients receiving MFNS alone had lower postnasal drip score in comparison with those treating with Sinupret and MFNS.
This finding is not in accordance with lower rhinorrhea and mucopurulent secretion score in MFNS/Sinupret group after the treatment. Besides the fact that in patients with ARS/CRS clinical findings sometimes are not in accordance with subjective senses, this interesting phenomenon could be explained by strong secretolytic and secretomotoric activity of Sinupret. Dysfunctional mucociliary transport is a common pathophysiologic process developed as a result of infection and inflammation in ARS and CRS. Transport of mucus from the nasal cavity to the pharynx is influenced by the transepithelial secretion of ions, especially chloride ions (Cl⁻). Primary Cl⁻ channel in respiratory epithelium responsible for good mucociliary transport is the ‘cystic fibrosis transmembrane conductance regulator’ (CFTR), which is dysfunctional or absent in patients with cystic fibrosis resulting in a significant reduction of ciliary beat frequency.⁷,¹⁶ Improvement of mucociliary clearance represents an important therapeutic strategy for patients with sinusitis by accelerating clearance of inflammatory products and pathogenic bacteria. Bioflavonoids, the main pharmacological components in Sinupret, strongly activate transepithelial Cl⁻ secretion in airway epithelial cells resulting in hydration of airway surface liquid covering respiratory epithelia is influenced by the transepithelial secretion of ions, especially chloride ions (Cl⁻). Primary Cl⁻ channel in respiratory epithelium responsible for good mucociliary transport is the ‘cystic fibrosis transmembrane conductance regulator’ (CFTR), which is dysfunctional or absent in patients with cystic fibrosis resulting in a significant reduction of ciliary beat frequency.⁷,¹⁶ Therefore, Sinupret stimulates the ciliary beat frequency of human epithelial cells in vitro, with a significant increase only 10 minutes post-application and dose-dependent effects lasting up to 1 hour.⁸ So, in patients treated with Sinupret and MFNS, accelerate nasal fluid clearance and low nasal secretion viscosity annul the inhibitory corticosteroid effects on mucosal gland secretion and inflammatory exudation, resulting in subjective sense of increased postnasal drip. Accordingly, the patients with combined therapy have higher postnasal drip score in the post-treatment period in comparison to ARS patients treated only by MFNS.

We observed no adverse events in patients from MFNS/Sinupret group in contrary to two participants from MFNS group which had the mild epistaxis and atrophic and destructive changes of the ciliated epithelium. This could be an explanation of a protective role of Sinupret in combined treatment of ARS.

**Conclusion**

Our results demonstrated better efficacy of combined MFNS/Sinupret therapy on nasal obstruction, rhinorrhea, facial pain/pressure and impaired sense of smell, as well as on endoscopic findings in patients with ARS in comparison to MFNS monotherapy. The absence of adverse events suggests a better safety of combined treatment comparing to nasal corticosteroid monotherapy in patients with uncomplicated form of ARS.

**Conflict of Interest:** No conflicts declared.

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