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EVIDENCE-BASED MANAGEMENT OF ACUTE RHINOSINUSITIS WITH HERBAL PRODUCTS

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Abstract: The overuse of antibiotics for unjustified indications such as the management of acute uncomplicated rhinosinusitis has contributed to the emergence of antibiotic-resistant strains of bacteria and prompted the need for alternative treatments. This review assesses the quality of evidence for the management of acute rhinosinusitis with herbal products, with the goal of positioning them among other treatments and identifying future research directions. Searches with Nacetylcysteine and mometasone furoate nasal spray (MFNS) were performed to compare the strength of evidence of herbal products to these conventional products, which are indicated for acute rhinosinusitis.

Keywords: Acute rhinosinusitis, Herbal product, Conventional treatment, Antibiotic

Introduction

Acute rhinosinusitis, a common infection of the upper respiratory tract, is associated with a significant impact on quality of life and high socioeconomic costs [1]. Guidance on the treatment of acute rhinosinusitis is clear. The European position paper on rhinosinusitis and nasal polyps (EPOS) 2012 recommends antibiotics for sinusitis of bacterial origin only , and the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR:RS) recommends a conservative approach to the use of antibiotics on the grounds that acute rhinosinusitis even of bacterial origin has a high spontaneous resolution rate. In cases of acute viral rhinosinusitis, guidelines support the use of topical steroids, antihistamines and ipratropium bromide (level of evidence Ia), aspirin/non-steroidal anti-inflammatory drug (level of evidence Ib), and herbal medicines (level of evidence Ib). Systemic steroids, however, are only rec ommended in complicated sinusitis [2].

Despite the existence of these recommendations on the use of antibiotics, acute rhinosinusitis is frequently treated with antibiotics, contributing to the global emergence of antibiotic-resistant strains of bacteria . One way of addressing the overuse of antibiotics in this scenario is to identify alternative treatments for rhinosinusitis that treat the infection and control symptoms.

Herbal products first triggered the interest of clinicians in the 1990s, and there has been a drive to perform fur ther studies on them ever since . Until the 1990s, evidence for the use of herbal products in acute rhinosinusitis remained largely anecdotal. However, in the past 20 years, randomized controlled trials in rhinosinusitis have been performed with a number of herbal products . This review aims to assess the level and quality of evidence for the management of acute rhinosinusitis with herbal products and review their position in the context of other treatments. To this end, we have selected four herbal products for which

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high-level evidence was available from at least one double-blind randomized clinical trial involving approximately 100 patients or more, either versus placebo or in comparison with another active treatment: Sinupret®, Pelargonium sidoides extract, Cyclamen europaeum (CE), cineole, and GeloMyrtol forte®.

To provide context for these data, we compared the strength of evidence of herbal products with that of the two synthetic treatments currently indicated for the management of acute rhinosinusitis, N-acetylcysteine and mometasone furoate. [3].

The structure of the search strings was 'acute rhinosiusitis' or 'acute rhinitis' or 'acute sinusitis' and '[product name]'. The search was intended to identify randomized controlled trials, however, when none were available, other study types were included.

Sinupret versus placebo Neubauer and März tested the efficacy and toxicity of Sinupret (BNO 101) in a randomized double-blind placebo-controlled trial . The trial included 160 patients with a diagnosis of acute bacterial sinusitis (n = 81in the Sinupret group and n = 79 in the placebo group).Sinupret or placebo were given as two sugar-coated tablets three times a day for 2 weeks alongside an antibiotic and a decongestant. Overall, patients in the Sinupret group had significantly better primary outcomes – radiographic findings and patient assessment of the therapy at the end of treatment – than patients receiving placebo.Likewise, patients in the Sinupret group reported a significant improvement in secondary outcomes, including mucosal swelling, nasal obstruction and headache, compared with patients in the placebo group. No significant toxicities were reported in either study group. The main limitation of this trial was the inclusion of male participants only.A meta-analysis by Melzer et al., including publishedand unpublished data with BNO 101, confirmed the results of the trial [4].

The studies included in the meta analysis also had a predominantly male population, limiting the application of the findings to a broader population.Similar benefits of Sinupret (BNO 1016) were reportedin patients with acute viral rhinosinusitis, in a robustly designed double-blind randomized controlled trial .In contrast to the trial conducted by Neubauer and März,patients did not receive treatments for acute rhinosinusitis other than the study drug, and there was a higher proportion of women than men in both treatment groups [5].

This trial randomized 386 patients (n = 194 in the Sinupret group and n = 192 in the placebo group). Patients received two tablets of Sinupret 80 mg or placebo, three

times daily for 15 days. In the intent-to-treat (ITT) population (n = 190 in each group), the number of patientsconsidered to be healed (investigator-assessed major symptom score [MSS] ≤ 1) was significantly higher in the Sinupret group than in the placebo group (48.4% vs.35.8%; p = 0.0063) at the end of treatment. The numberneeded to treat (NNT) for patients to have MSS ≤ 1 at theend of treatment was eight in the ITT. This result wascorroborated by patient-assessed MSS, the 20-item questionnaire sino-nasal outcome test (SNOT-20) German adapted version (GAV), and ultrasonography imaging.The incidence of adverse events was similar between the two groups. The per-protocol (PP) analysis of the trial gave results concurrent with the ITT analysis [6].

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In summary, adequately powered randomized trials have demonstrated superiority of Sinupret versus placebo in patients with bacterial or viral rhinosinusitis.Trials of Sinupret in bacterial sinusitis almost exclusively included male patients, while trials of Sinupret in viral sinusitis included a mixed-gender study population.Sinupret versus other treatments A limited number of studies have provided evidence on the efficacy and safety of Sinupret versus synthetic treatments. The literature search identified one open-label study comparing Sinupret Forte with intranasal fluticasone furoate . Sinupret Forte (one tablet) was given three times a day while fluticasone

furoate (two puffs in each nostrils) was given once a day for 14 days. Both Sinupret and intranasal fluticasone in duced a similar improvement in MSS and SNOT-20 as

evaluated by the investigator at Day 14. Patients in the Sinupret Forte group did not report any adverse events.In the fluticasone group, one patient reported epistaxisand two patients reported nasal itching. The conclusions of the study are limited by its relatively small size and open-label design.Another study compared a combination of Sinupret and Cinnabaris 3X with synthetic treatment, including antibiotics, secretolytics and sympathomimetics in patients presenting with acute sinusitis or an acute exacer bation of a chronically relapsing sinusitis [7].

Overall, robust head-to-head comparisons of Sinupret with conventional treatments are currently not available.Published studies lack statistical power or were not de signed to show either differences or equivalence between treatments, thereby limiting the strength of conclusions.

Cyclamen europaeum (CE)

CE extract has been used for a long time in Southeast Europe for the management of nasopharyngeal diseases. However, the first randomized trials assessing theefficacy and safety of this product in acute rhinosinusitis became available very recently only . In itscurrent formulation, the aqueous/alcohol CE extractcontains the saponin fraction [8]. When administered intranasally, the extract causes a rapid, abundant and often painful discharge of mucus through a cholinergicreflex lasting for about 30 min . The literature search identified two double-blind randomized trials comparing CE nasal spray with matching placebo in acute rhinosinusitis. These two trials were subsequently included in a Cochrane meta-analysis aiming to assess the efficacy and safety of CE nasal spray in acute rhinosi nusitis. Studies with CE extract are summarized in Overall, both trials have reported a consistent lack of effect of nasal CE on sinusitis symptoms and did not have adequate statistical power to provide robust con clusions about the safety and efficacy of CE nasal spray.It is also possible that the immediate irritative effect of CE might have compromised the blinding of treatment in both trials. [9].

This meta-analysis found an overall low risk of selection,performance and detection bias in the two studies in cluded. The authors also emphasized the need for fur ther randomized controlled trials to evaluate the efficacy of this treatment for acute rhinosinusitis [10].

Baseline characteristics suchas age, gender, weight, symptoms-sum-score, allergy and smoking status, were balanced between the two Comparative studies of herbal products Data

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from head-to-head comparisons can help guide treatment decisions and help clinicians to make evidence based decisions. Equivalence or superiority of one product versus another cannot be assumed based on cross-study comparisons and must rely on direct, comparative data.The literature search identified one randomized trial and one non-interventional study comparing herbal medicines [11].

Tesche and colleagues conducted a double-blind randomized trial comparing a herbal preparation containing five components, possibly resembling Sinupret, with cineole .Of note, this study did not clearly state using Sinupret when refering to the composition of the preparation. Furthermore,no placebo group was included in the study. The study recruited a total of 150 patients across three centres, with 75patients randomized to each treatment group. Likewise, cineole induced a greater improvement than the other preparation in each individual component of the symptom

sum score at Days 4 and 7. Improvement at Day 7 in redness of mucosa, oedema and dryness was greater with cineole than with the other preparation, confirming the effect observed on the symptom-sum score. Two patients in the cineole group and three patients in the other group reported mild side effects.Sinupret (BNO 1016) was compared with GeloMyrtol in anon-interventional parallel group study [12].The study reported comparable effectiveness of the two treatments on acute rhinosinusitis symptoms, with amore rapid recovery of facial pain with GeloMyrtol than with Sinupret. However, the study presents a significant number of weaknesses in its design and methodological approach. For example, the design is closer to that of a randomized controlledtrial, and the analysis lacks the statistical support of a randomized trial such as predetermined endpoints [13].

Overall, there are few head-to-head studies of herbal products. Only one randomized double-blind trial has compareda herbal preparation containing five components resembling Sinupret with cineole, while another study comparing GeloMyrtol with Sinupret is associated with serious methodological flaws. There is a need for further randomized comparative trials with herbal products to differentiate and delineate the properties of each product.Conventional treatments for acute rhinosinusitis Mometasone furoate nasal spray versus placebo or amoxicillin Mometasone furoate nasal spray (MFNS) has been usedsince 1998 for the management of inflammatory diseases of the nose [14].

Mometasone furoate is a glucocorticosteroid indicated for rhinitis and acute rhinosinusitis in some countries, as well as several other conditions including asthma, skin disorders, and phimosis . In acute rhinosinusitis, the anti-inflammatory properties of mometasone furoate are thought to mediate its benefi cial effects . The literature search identified three clinical trials of mometasone furoate in acute rhinosinusitis,one Cochrane meta-analysis, and two exploratory analyses of the same trial. However, symptoms such as rhinorrhea, post-nasal drip, or cough were not significantly different between the MFNS and placebo groups. In both treatment groups, most adverse events were mild or moderate.Minimizing the systemic activity of intranasal steroids is an important consideration to reduce the risk of hypo thalamic pituitary adrenal (HPA) axis suppression. The differences between the three groups persisted from baseline to Day 21. Likewise, individual symptom scores such as congestion, facial pain, rhinorrhea and post-nasal drip showed greater improvement with MFNS than with placebo.Most adverse events were mild or moderate in intensity,

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but included headache and epistaxis [15].

Most adverse events were mild or moderate and considered to be related to study drugs. Exploratory analyses of this trial showed that MFNS twice daily was associated with better quality of life scores than placebo and more minimal symptom days than placebo or amoxicillin . Improved efficacy with the higher dose of MFNS was confirmed in a Cochrane meta-analysis [16].

N-acetylcysteine versus placebo Currently, the two main indications for N-acetylcysteine are chronic obstructive pulmonary disease and paracetamol overdose . It is also of potential interest for the management of acute rhinosinusitis due to its antimicrobial activity, ability to interfere with biofilm formation, and its mucolytic and antioxidant action [17].

The authors found that N acetylcysteine did not affect the Lund-Mackay scoreused for radiologic staging of sinusitis and it was concluded that the addition of N-acetylcysteine to conventional treatment has no benefits in acute sinusitis.In another trial, where only the investigators wereblinded to treatment, N-acetylcysteine was comparedwith ambroxol, another secretolytic agent [18]. In the ITT population, the improvement in sinusitis-related symptoms was greater in the N-acetylcysteine group than in the ambroxol group.The authors reported a higher proportion of patients with improvement at the end of treatment in the N acetylcysteine group (82.67%) than in the ambroxolgroup (50.67%) ($p < 0.0001$). At Months 3 and 6, the number of rhinosinusitis exacerbations after the previous episode was also lower in the N-acetylcysteine group than in the ambroxol group. The proportion of patients reporting adverse events was lower in the N acetylcysteine group (18.67%) than in the ambroxol group (52%). The main limitations of this study relate to its open-label design, the lack of clearly defined end points, and the lack of comparability of both treatment groups at baseline.Overall, evidence for the use of N-acetylcysteine in acute rhinosinusitis is limited to small-scale clinical trialswhose designs do not enable firm conclusions on the efficacy of N-acetylcysteine in this indication[19].

Conclusion

A range of herbal products have been evaluated for treating acute rhinosinusitis in randomized clinical trials.Sinupret is supported with the strongest evidence base,including adequately powered multicenter clinical trials,followed by EPs 7630, which is supported by smallerstudies. Across the range of other herbal products, including CE nasal spray, GeloMyrtol, and cineole, only one randomized trial is available at best for each product. Furthermore, each trial identified in this review was

conducted in a single country without power calculations and a small number of participants. Ideally, ad equately powered international multicenter trials wouldbe required to confirm or discredit findings and provide further credibility for these products[20].Among synthetic treatments described in this review,MFNS is supported with the strongest evidence. Interestingly, the evidence for Sinupret appears to be as

strong as that for synthetic treatments, such as MFNS.Although cross-trial comparisons cannot be a substitutefor direct comparisons, clinical trials of Sinupret and MFNS suggest comparable efficacy of these two products. However, patients may prefer the herbal over

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the‘steroid’ approach.The choice between synthetic treatment or herbal medicine is made difficult by the lack of comparative studies of herbal products with conventional medicines.Indeed, most trials conducted with herbal products have been placebo-controlled trials. Currently, only one underpowered study comparing Sinupret with fluticasone furoate is available [21]. Equally, there are not enough data of sufficient quality available to guide anevidence-based approach when choosing between different herbal products. To the best of our knowledge, only one head-to-head comparison of herbal products isavailable, stressing the need for further prospective trials comparing herbal products [22]. A separate study comparing Sinupret with GeloMyrtol does not allow a firm conclusion to be drawn on the efficacy of either product,due to its design [23].

Sinupret (BNO 1016) is the sole herbal product forwhich evidence from well-designed, randomized controlled studies with sufficient power is available. In the context of antibiotics misuse, selected herbal medicines are promising alternatives to conventional treatments and should be considered for the management of acute uncomplicated rhinosinusitis[24].

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