Laryngorhinootologie

Journal for ENT Therapy, Head and Neck Surgery
Combined with Monthly Journal for ENT Therapy and Practice

Efficacy of Myrtol Standardized in the Therapy of Acute Sinusitis – Results of a Double-Blind, Randomized, Placebo-Controlled, Multicentric Study²

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Summary. Background: In the management of non-purulent acute sinusitis, α-adrenergic substances are administered topically and secretolytics systemically. Antibiotic therapy should be restricted to purulent forms. This study was designed to demonstrate the importance of the maintenance of permanent ventilation and drainage of the sinuses as a therapeutic concept. Patients/Methods: In this multicentric study the efficacy and safety of myrtol standardized and another essential oil were investigated in 331 patients with acute sinusitis in comparison to placebo. 330 patients were evaluated in an intent-to-treat analysis and 291 patients remained for statistical analysis. The study was conducted in 16 centers in a double-blind, double-dummy, randomized design versus placebo. During an observation period of 14 days the patients were treated for 6 ± 2 days with the respective study medication. Results: With respect to efficacy, both myrtol standardized and the other essential oil proved to be significantly superior to placebo. As to the tolerance, a slight advantage of myrtol standardized was demonstrated in comparison to the other test substance. Conclusion: These results support the value of essential oils like myrtol standardized as an effective treatment in acute, uncomplicated sinusitis instead of antibiotics as first choice.

Key words: Acute sinusitis – Secretolytics – Myrtol standardized – Essential oils

Introduction

In general medicine acute sinusitis is a very frequently occurring clinical situation. In most cases it results from a viral infection which leads to mucosal edema and the increased production of a secretion with changed properties; this, in turn, results in an impairment of mucociliary transport as a self-cleansing mechanism [1]. Mucosal stasis occurs and the paranasal ostia are obstructed. This favors bacterial superinfections which, in turn, may lead to severe complications and finally to chronicization of the sinusitis [3]. Although the spontaneous healing rate of viral sinusitis is high, a primary, symptomatic therapy with secretolytic/secretomotor substances as well as with decongestive agents is indicated in order to prevent further progression of the disease [3, 5, 6, 12].

Myrtol standardized has been used for years in the treatment of acute and chronic sinusitis [7, 8, 10]. After enteric absorption it is mainly secreted via the bronchial mucus membranes. Myrtol standardized has secretolytic and secretomotor properties by way of increased mucociliary clearance. In addition anti-inflammatory and antibacterial activities have been reported [9].

The diagnosis sinusitis is based on clinical findings [1, 3]. A purulent sinusitis, which requires the use of antibiotics, can also be assumed when, for example, the complaints last for more than one week [3, 4] and are very severe or, respectively, there is danger of complications [4].

Acute sinusitis has a series of characteristic symptoms such as headache, which can become more intense when the head is bent forward, impairment of the general condition, fever, pressure sensitivity at the exit of the trigeminal nerve, changes in nasal secretions, and disturbed nasal breathing.

The modified form of a symptom score based on the above symptoms was developed in cooperation with Prof. Burian, Vienna, to evaluate the severity and course of acute sinusitis under therapy and was tested on a representative patient collective.

Patients and Methods

The study was carried out in a double blind (double dummy) randomized design in 16 centers. 331 out-patients over 18 years of age with the test diagnosis of acute sinusitis were enrolled after being informed by the responsible physician and having given their written consent. Exclusion criteria to be observed were: the necessity for antibiotic administration at the start of the study, dry sinusitis, pregnancy and nursing, severe accompanying diseases of the liver, kidney, lungs, metabolism, or blood picture, consumption of antibiotics in the previous

1 Gelomyrtol forte, G. Pohl-Boskamp.
four weeks, peptic ulcer, other accompanying diseases that could adversely affect the performance of the study, operations planned for the study period, known hypersensitivity to essential oils, alcohol and/or drug abuse, lack of compliance, as well as participation in another clinical study within the preceding four weeks.

In the first examination the patients' sex, age, height, ethnic grouping were recorded. At the same time their vital parameters, weight, body temperature, blood pressure and pulse rate in the sitting position were determined.

The severity of the sinusitis was assessed by means of a symptom score; for acute sinusitis the characteristic symptoms (headache, pain on bending with the head bent forward, impairment of general condition, pressure sensitivity in the trigeminal region, nasal secretion, amount and viscosity of secretion, as well as disturbed nasal respiration) were scored in the range 0 to 3. Ten of the 25 maximally possible points were required for inclusion.

Thereafter the patients received the test substances consisting either of myrtol standardized (300 mg, yellow capsules, Gelomyrtol® forte), another essential oil not registered for the indication (300 mg, green capsules), and placebo (yellow and green capsules). The drugs for each patient were packed in boxes containing 8 sealed blister strips each containing 8 capsules. Depending on the randomization, the blister strips contained 4 capsules of test drug and 4 capsules of placebo or 8 capsules of placebo. One yellow and one green capsule were to be taken four times daily. In addition the patients were given a xylometazoline metered dose aerosol with which 4 × 2 puffs were to be administered to each nostril daily. Other nasal drops and any additional therapy for the test indication (e.g. local thermal therapy, inhalations) were not permitted. The test medication was taken for 6 ± 2 days, thereafter the patients were seen again.

At the second visit the test and accompanying agents were returned, the symptom score was assessed, a possibly required further treatment of the sinusitis was documented, undesired events were recorded, and a change in the accompanying treatment decided. At a control visit after another week (day 13 ± 2) the patients were questioned on a possible reinfection and its treatment, any occurring undesired events, and changes in the accompanying medication.

Legal and Ethical Aspects

The planning and performance of the study were in accordance with the relevant guidelines of Germany (AMG) and the EU recommendations for Good Clinical Practice.

Statistical Methods

The object of the study was to evaluate the superiority of myr- tol standardized and/or another – but not registered for this indication – essential oil (designated hereafter as e.o.) against placebo on the basis of the symptom score before and after treatment, the need for antibiotics, and the necessity for further treatment. The differences between the symptom scores before and after therapy were evaluated by an analysis of covariance. All other variables were evaluated descriptively.

Results

In the course of the study the following violations of the test plan were found: one patient had demonstrably not taken the test substance, 4 patients were non-compliant, 28 patients had not used the obligatory xylometazoline spray. 3 patients did not have a symptom score at the second visit, 1 patient took antibiotics during the study period, 1 patient did not complete the study period, and in one further patient the active principle of the test drug (myrtol standardized) had been taken prior to the study period. Thus, of the 331 patients enrolled in the study 330 were available for the intent-to-treat analysis and 291 for the efficacy analysis. In the three treatment groups the following numbers of patients were legitimate for the intent-to-treat analysis: 109 patients in the myrtol standardized group, 110 patients in the e.o. group, and 111 patients in the placebo group while 94 patients of the myrtol standardized group, 97 patients in the e.o. group, and 100 patients in the placebo group were available for the efficacy analysis.

With respect to the demographic data there were no relevant differences between the two collectives and the three treatment groups. Female patients predominated with about 60%; this was reflected in all treatment groups to varying degrees. Neither were there clinically relevant differences between the two collectives and the three treatment groups with regard to the vital parameters weight, body temperature, blood pressure, and pulse rate.

Conspicuous accompanying physical findings of cardiovascu- lar diseases were found more frequently in the e.o. group, of the locomotor system in the myrtol standardized group, and of the eyes in both test substance groups. The risk factors smoking and alcohol were somewhat less frequent in the placebo group than in the two test substance groups.

Prior to commencement of the therapy the symptom scores as a measure for the severity of the disease were practically identical for all three treatment groups. Neither were there relevant deviations with regard to the secondary efficacy covariables “duration of illness” and “duration of treatment”. On the whole, a generally good comparability between the three treatment groups was observed. There was an increased use of cough and cold preparations as prior and accompanying medication (42.3%) in the placebo group as compared to the two test substance groups. During the average treatment of 7 days the compliance of the patients was generally estimated to be good.

The symptom scores under treatment in the two test substance groups as compared to the placebo group changed significantly during the therapy (p = 0.02 in the intent-to-treat groups [n = 326] and p = 0.03 for the efficacy analysis group [n = 291]). The differences in scores between visit 1 and visit 2 were on average 10.3 points for the myrtol standardized group, 10.6 points for the e.o. group, and merely 9.0 points for the placebo group in the intent-to-treat population; the corresponding values in the efficacy analysis population were 10.5, 10.9, and 9.2 points, respectively.

Statistically a superiority of the myrtol standardized therapy and the essential oil therapy as compared to placebo treatment has been demonstrated.
After the therapy period further treatment with antibiotics was necessary in 38 patients, 15 (40%) of these were from the placebo group, 14 (37%) from the e.o. group, and only 9 (23%) from the myrtol standardized group. A renewed infection was detected in 4 patients at the final control visit, 3 of these were from the placebo group.

82 patients reported eleven different kinds of adverse events. In no case the adverse events were classified as serious. The most frequent event with 39 reports involved the gastrointestinal tract; about half of these (19 reports) were from the e.o. treatment group while 12 were from the myrtol standardized group and 8 from the placebo group. Also with regard to severity the e.o. group dominated with 72.7% of the undesired events classified as being of medium intensity as compared to 63.4% classified as being of mild intensity in the myrtol standardized group. In total, four events were assessed as severe, 3 of these being in the placebo group. Also the more or less equal distribution of undesired events in the three treatment groups, including the placebo group, minimizes the clinical relevance of the events.

In most cases (85.6%) no interventions with respect to the test medication were necessary. However, it is conspicuous that in 10 out of 33 cases under therapy with e.o. the test medication was discontinued; this occurred in only 3 cases under myrtol standardized and in 2 cases under placebo.

The occurrence of 28 adverse events was considered to be in direct temporal relationship with the administration of the test agents. They could be included in the expected side-effect spectrum for the test agents and were thus classified as adverse drug reactions. 16 of these events were attributed to e.o. and 12 to myrtol standardized. The major proportion (23 cases) affected the digestive system: 9 were reported by the myrtol standardized group and 14 by the e.o. group as adverse drug reactions and included eructation (3/1), feeling of satiety (1/0), nausea (1/3), pyrosis (1/1), diarrhea (1/3), meteorism (1/0), constipation (1/1), stomach pain (0/2), stomach cramps (0/2), and epigastric pain (0/1).

In summary, the number and nature of the adverse reactions emphasize the generally very good tolerability of the test substances. On considering the adverse drug reactions individually, the superiority of myrtol standardized over the other e.o. that is not registered for this indication is apparent.

Discussion

All the patients with acute, uncomplicated sinusitis examined in this study were treated under the same basic therapy with a substance (xylometazoline) for decongesting the nasal mucosa. At the same time we wanted to test the hypothesis whether clinically relevant therapeutic results for the maintenance or restitution of ventilation could be achieved by the additional administration of myrtol standardized or of the other e.o. with secretolytic activity but not registered for this indication.

The severity and course of acute sinusitis were evaluated under the three therapy regimens by means of a symptom score developed and validated for this study. The symptom score weights and correlates the characteristic symptoms of acute sinusitis. The entry criteria for enrollment in this study ensured that patients with banal rhinitis or dry, chronic sinusitis were not included in the study.

In spite of an effective decongestion with xylometazoline, an additional, statistically significant therapeutic superiority success was demonstrated on the basis of the symptom score in both test substance groups during the observation period. It was thus shown that the principle of restitution of ventilation and drainage, represented by the treatment of uncomplicated, acute sinusitis with decongestive and secretolytic substances, effectively leads to a rapid elimination of the symptoms in patients with this syndrome.

It is now well established that a viral infection of the upper respiratory tract with the consequence of congestion in the region of the osteomeatal unit and decreased mucociliary clearance in the region of the paranasal sinuses paves the way to a major extent for the subsequent development of acute, purulent sinusitis [6]. A prevalence of 1.4% [3] or respectively 1 in 200 cases for acute cold [1] can be assumed.

Therapy recommendations in the field of otolaryngology recognize an indication for antibiotic therapy for acute bacterial rhinosinusitis only in the following circumstances [5]:
1. patients with severe complaints,
2. threat of complications (orbital, intracranial, osteomyelitis),
3. small children,
4. children with recurrent tubal catarrh,
5. patients with chronic bronchitis,
6. immunodeficient or immunosuppressed patients,
7. geriatric patient groups,
8. patients with cachetic diseases.

The pathophysiologival features of the disease with mucostasis and the danger of a subsequent bacterial superinfection were taken into consideration in the study design. Based on the knowledge of the high restitution ability of the mucus membranes of the paranasal sinuses and consequent maintenance of ventilation and drainage, the test hypothesis of this clinical study on the secretolytic and secretomotor spectrum of action of myrtol standardized as well as the other e.o. was formulated and confirmed. The efficacy of myrtol standardized against placebo and in comparison with another substance that is not registered for the indication of acute sinusitis was therefore examined in a double blind study. The use of a decongestive nasal spray was an obligate accompanying therapy; no other supporting measures such as thermal or inhalation measures were allowed. In this way the highest possible comparability under objective evaluation criteria (symptom score) was ensured. The compliance of the patients with this therapy regimen can be considered as very good, as demonstrated by controlling the intake of the test substances.

In addition to a statistically significant improvement of the symptom score the therapeutic efficacy was also demonstrated by positive changes in the specific symptoms headache, nasal secretion and viscosity of the secretion (Fig. 1). The differences in favour of myrtol standardized against placebo were all in the range from 9 to 14%.

The results of this study are in agreement with previously published data according to which the therapy for uncomplicated sinusitis using only secretolytic and decongestive agents is jus-
written and spoken clearing up of the patients about possible side effects. Those accompanying events with a possible causal relationship to the use of the test substances were mostly of mild intensity and corresponded to the known side-effect spectrum of the administered substance. These findings on tolerability support the generally good to very good tolerance of plant-derived secretolytics reported in the literature. Gastrointestinal side effects were slightly more pronounced in the e.o. treatment group as reflected by the higher number of discontinuations of the test substance in this group (10 in the e.o., 3 in the myrtol standardized, and 2 in the placebo group).

In summary, we can conclude that this study has demonstrated the efficacy of myrtol standardized as well as that of the other e. o., that is not registered for this indication, in the treatment of uncomplicated, acute sinusitis in combination with a decongestive therapy. The benefit-risk ratio of the other e. o. is, however, slightly less favorable. Thus, treatment with myrtol standardized is a rational and pathophysiologically oriented alternative to the uncritical, early use of antibiotics or therapeutic nihilism of acute sinusitis.

References


Fig. 1  Symptom improvement

Fig. 2  Need for antibiotics after a treatment phase of 6 ± 2 days


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