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Efficacy and Tolerability of a Spray with *Salvia officinalis* in the Treatment of Acute Pharyngitis – A Randomised, Double-blind, Placebo-controlled Study with Adaptive Design and Interim Analysis

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Abstract
Objective: This randomised, double-blind, parallel group phase II/III study with adaptive two-stage design and interim analysis compared the efficacy and tolerability of spray (containing a *Salvia officinalis* fluid extract) against placebo in the treatment of patients with acute viral pharyngitis.
Study Participants: in two study parts, a total of 286 patients with subjective and objective evidence of pharyngitis were randomized. In the 1st study part 122 patients were enrolled. In the 2nd study part 164 patients were included. The treatment duration per patient was 3 days, including one baseline visit and one final visit.
Main Outcome Measures: Area under Curve for change of throat pain intensity (spontaneous pain), documented every 15 minutes within the first 2 hours after the first application as compared to baseline using a visual analog scale (VAS 100 mm).
Results: Following the interim analyses of the first study part the 15 % spray* containing 140 µl sage extract per dose was the most promising preparation for the 2nd study part (main study) whereas for the 30% and the 5% preparation results made superiority over placebo unlikely in the final analysis. Overall, the 15 % spray was significantly superior to placebo for the primary efficacy variable with regard to a reduction of the throat pain intensity score. Only minor side effects such as dry pharynx or burning of mild intensity were seen.
Conclusions: The efficacy and tolerability profile of a 15 % sage spray indicated that this preparation provides a convenient and safe treatment for patients with acute pharyngitis. A symptomatic relief occurred within the first two hours after first administration and was statistically significantly superior to placebo.

Key words: acute pharyngitis, sage extract, pharyngeal spray, clinical trial

Introduction

Acute pharyngitis is one of the most common illnesses for which patients go to see their doctor. The main clinical symptoms are sore throat, fever and malaise. In addition, odynophagia, dysphagia, and purulent exudates can be present (Marvez-Valls 1998, Bisno 2001). The most common causes are viral infections (see Table 1). Normally, the illness is mild and self-limiting but may worsen due to bacterial superinfection, most commonly by group A or group C β-hemolytic streptococci. Serious sequelae such as rheumatic fever or endocarditis may follow bacterial superinfection (Bisno 2001). Table 1 gives an overview of the different microbial causes of acute pharyngitis.

Because of these sequelae, bacterial causes of the pharyngitis must be ruled out or, if positive, be treated with antibiotics. However, due to the predominantly viral cause antibiotics have only a minor benefit upon the resolution of pharyngitis symptoms. Thus, in most cases the treatment of acute pharyngitis is symptomatic focussing on the management of fever and pain. Normally, because of its benign nature, symptomatic treatment can start immediately. Among a variety of substances which belong to the NSAID group (non-steroidal anti-inflammatory drugs), as a non chemically defined drug *Salvia officinalis* preparations may be beneficial due to their recommended use (Commission 1985 and 1990, ESCOP 1996 and 2003) which is supported by the documented anti-inflammatory, anti-nociceptive and astringent properties of sage compounds. Beneficial clinical experiences with sage preparations for the prophylaxis of oral mucositis also support their use in these conditions (Leitlinien Supportive Therapie 2002).

Therefore, to support the indication acute pharyngitis a clinical trial was performed details of which will be presented in this paper.

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Table 1. Microbial causes of acute pharyngitis (modified acc. to BISNO 2001).

viral pathogens	bacterial pathogens	Chlamydiae	Mykoplasmae
Rhinovirus	Streptococcus pyogenes	Chlamydia pneumoniae	Mycoplasma
Coronavirus	(group A β-hemolytic streptococci)		pneumoniae
Adenovirus	Group C β-hemolytic		
Herpes simplex virus	streptococci		
Parainfluenza virus	Neisseria gonorrhoeae		
Influenzavirus	Corynebacterium diphteriae		
Coxsackievirus	Aranobacterium		
Epstein-Barr virus	haemolyticum		
Cytomegalovirus			
Human			
immunodeficiency			
virus type 1			

Product Profile

Salvia officinalis L., also known as Dalmatian sage, belongs to the Lamiaceae family. The genus Salvia comprises 500 - 900 species (Hager 2004). Many of them, e.g. *Salvia officinalis*, *S. triloba*, *S. divinorum*, *S. lavandulifolia, S. miltiorrhiza*, are used therapeutically. In addition, different sage preparations are also used as spices or food antioxidants.

The parts of the plant mainly used for therapeutic purposes are the leaves, which have a monograph each from the Commission E and ESCOP (Commission E 1985 and 1990, ESCOP 2003). Today, the medicinal use of *Salvia officinalis* preparations in Germany is based on the Commission E monograph (Commission E 1985 and 1990) and on the German Standard License (Standardzulassungen 1996) for sage leaf infusion.

Salvia preparations are used internally for dyspeptical complaints and hyperhidrosis of different etiology. The external application comprises the treatment of inflammation of the oral and pharyngeal mucosa, gingivitis or pressure points of the denture. Furthermore, traditional use includes gastropathy, loss of apetite, meteorism, diarrhea and enteritis. Sage preparations were already applied in ancient times (Lippmann and Wegener 2001): thus, the traditional experience comprises several thousend years of internal and external application.

Different sage preparations exhibited bactericidal, fungicidal and antiviral activities in vitro. Rosmarinic acid, an important constituent of sage, was shown to have anti-inflammtory properties (ESCOP 1996). These anti-inflammatory activities could be confirmed in in vivo experiments (ESCOP 2003). Pharmacokinetic data following oral application of sage extracts are not available. Following the monographs, sage preparations do not show undesirable effects (ESCOP 2003).

Salvia officinalis contains 1 - 2,5 % of essential oil which consists mainly of thujone (ca. 35 - 60 %), furthermore cineol, camphor, borneol, bornylacetat, camphen, linalool, α- und β-pinen, viridiflorol, α- und β–caryophyllen. Non-volatile substances are tannins (3 - 7 %), e. g. rosmarinic acid, and the bitter diterpenes carnosol und salvin. The flavonoid content of sage leaf is ca. 1 - 3 %. Furthermore triterpenes, predominantly ursolic acid and oleanolic acid, have been described (Commission E 1985 und 1990, Pachaly 1990, Hager 2004). Thujone, the major component of sage oil, is known to be toxic (Hager 2004). However, thujone concentrations in licensed medicinal products based on the provisions of the official monographs are uncritical. No side effects of such products related to thujone have been reported.

Valverde® Salvia Rachenspray is a new medicinal product presented as a pump spray in a glass flacon. The therapeutically active principle is a sage leaf fluid extract (1:1, extraction solvent ethanol 70 % [V/V]. The product contains 15 % of the extract in an aqueous solution. The droplet size is 50 – 60 μm, thus big enough not to pass into the lower respiratory tract. One glass flacon holds 12 ml of the solution. Placebo was identically composed regarding ethanol and excipient concentration. It contained a pharmacologically inactive amount of 0.3% sage leaf extract for appropriate blinding.

Per single application, three puffs (= 3 times a metered dose of 140 μl) will be taken, the maximum use is three applications per day. The product is claimed for the short term treatment of acute pharyngitis.

To our knowledge, there are no similar approved products available on the European market. Thus, spray will be the first market entry within Europe.

Methods

Study Participants

This randomised, double-blind, placebo-controlled, multicentre, parallel-group study with adaptive design and interim analysis compared three different concentrations of spray with placebo in the 1st study part. Between December 2001 and February 2002 altogether 122 patients were recruited from 16 centers (n = 31 on the 30 % spray, n = 31 on the 15 % spray, n = 30 on

the 5 % spray, n = 30 on placebo). During the interim analysis a sample-size re-assessment was done, based on the treatment effect observed in the first study part. Further 80 patients per group were to be recruited. Actually, in the 2nd study part (main study) 164 patients from 21 centers were included from April 2002 until June 2002 (n = 82 on the 15 % spray and n = 82 on placebo). Male and female patients aged 18 years and older with symptoms of acute pharyngitis existing for max. 48 hours were eligible for participation in this study. The patients required typical signs (spontaneous pain, local inflammation) of pharyngitis confirmed by the study physician. Additionally, all participants had to document their spontaneous pain intensitiy on a visual analog scale (VAS) (to be eligible a minimum value of 40 mm was necessary on a VAS 100 mm). They were excluded from study participation in case of a positive test on group A β-hemolytic streptococci, concomitant illnesses as rhinosinusitis, laryngitis, tracheitis, bronchitis, fever, wounds or other significant changes in the oral cave, unallowed comedication, other pain situations like dental or tumor pain, requiring the intake of analgetic medication, operations in the oropharynx area up to 4 weeks prior to the study, seizures, or any known hypersensitivity against the study medication. Furthermore, pregnant or lactating women and women of childbearing potential who were not taking adequate contraceptive precautions were excluded. The 1st study part was conducted at 16 doctor's offices, in the 2nd study part 21 doctor's offices were involved.

Written informed consent was obtained from each patient. The study protocol was approved by the Human Ethics Commitee at the University of Munich and was conducted in accordance with the Declaration of Helsinki and the European guidelines for Good Clinical Practice.

Study Design

Two visits per patient were to be done. At the first visit, following informed consent and check of the inclusion and exclusion citeria, the diagnosis acute pharyngitis was confirmed by the treating physician. During the first 2 hours the patient had to stay in the doctor's office. Prior to the first application of 3 puffs spontaneous throat pain was estimated by the patient on a 100 mm VAS for baseline value (at least 40 mm necessary for inclusion in the study). During the first 2 hours pain intensitiy was assessed every 15 minutes and documented accordingly in a pain diary in the doctor's office. Thereafter, all subsequent pain measurements were done and documented accordingly at home in the pain diary the use of which was explained previously by the study personal. The following treatment phase consisted of two more applications on treatment day one, three applications on day two and one last application in the morning before the final visit. All applications were made up of 3 puffs each.

Efficacy and Tolerability Measurements

The primary efficacy variable in both study parts was the change of throat pain intensity (spontaneous pain), documented every 15 minutes within the first 2 hours after the first application as compared to baseline using the 100 mm VAS; the area under the curve (AUC) of the pain intensity differences (PID) was assessed.

The secondary endpoints in both study parts were:

- meaningful pain relief (MPR): max. 50 % of the baseline value on VAS
- complete pain reduction after first application
- change of throat pain intensity during study treatment (according to patient's diary)
- number of patients with early treatment discontinuation due to lack off efficacy
- overall efficacy assessment both by the physician and by the patient
- overall safety assessment both by the physician and by the patient
- adverse events (AE)

The statistical evaluation of secondary endpoints was done after the completion of the 2nd study part.

Statistical Analysis

Superiority vs. placebo for the three salvia preparations was tested in an adaptive two-stage design according to Bauer/Köhne. In the interim analysis each salvia preparation was compared to placebo via Wilcoxon-Mann-Whitney-U-Tests. Of the doses showing promising results only one dose was to be selected for the second study stage and to be compared versus placebo thereafter.

To control the overall type I error rate (2.5% one-sided) a bonferroni adjustment was used. The stopping boundaries in the interim analyses were α_1 = 0.00365 (success) and α_0 = 0.3 (futility). The critical value for the combination test was c_α = 0.001062.

Descriptive anaylsis: Mean and 95 % Confidence Intervalls (CIs) were determined in the AUC (PID) by treatment groups and the differences in the AUC (PID) between treatment groups.

Collectives: per-protocol collective (PP) was chosen for primary analysis; the full analysis collective (FAS) for used for secondary analysis; all missing values were determined by the Last Observation Carried Forward-(LOCF)-method.

Results

Patient Demographics

A total of 286 patients were randomised to treatment with spray or placebo. The distribution can be seen in Table 2.

Treatment groups were generally well matched for demographic and baseline clinical features. Although the patient collective in the 15 % group appeared to be slightly younger than in the other groups there was no statistically significant difference among the treatment groups.

Table 2.

Part 1	**Verum SII (30 %)**	**Verum S2 (15 %)**	**Verum S3 (5 %)**	**Placebo**
patients total	n = 31	n = 31	n = 30	n = 30
Male	10	15	11	10
Female	21	16	19	20
mean age	42.7	36.0	40.9	40.1
	(range 20 - 77) yrs.	(range 18-70) yrs.	(range 20-77) yrs.	(range 19-78) yrs.

Part 2	**Verum S2 (15 %)**	**Placebo**
patients total	n = 82	n = 82
Male	24	31
Fernale	58	51
mean age	44.1	41.2
	(range 18-00) yrs.	(range 19-86) yrs.

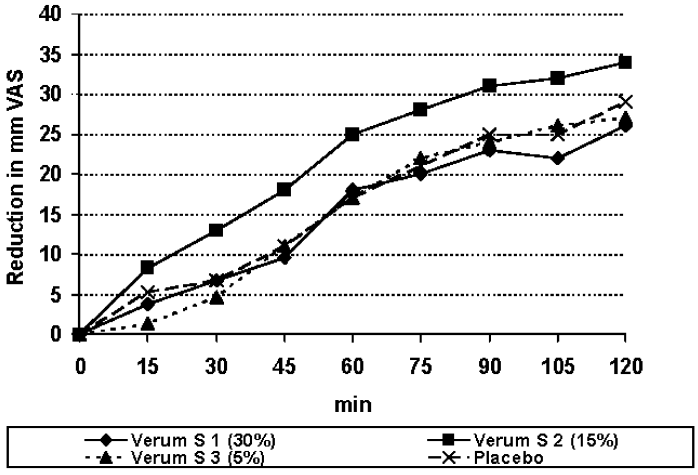

Fig. 1. Following paired comparison of the AUCs of PID versus placebo, the p-vaiues were as follows (for study part 1): Verum Sl (30 % m/m) vs. placebo: p = 0.475; Verum S2 (15 % m/m) vs. placebo: p = 0.093; Verum S3 (5 % m/m) vs. placebo: p = 0.420.

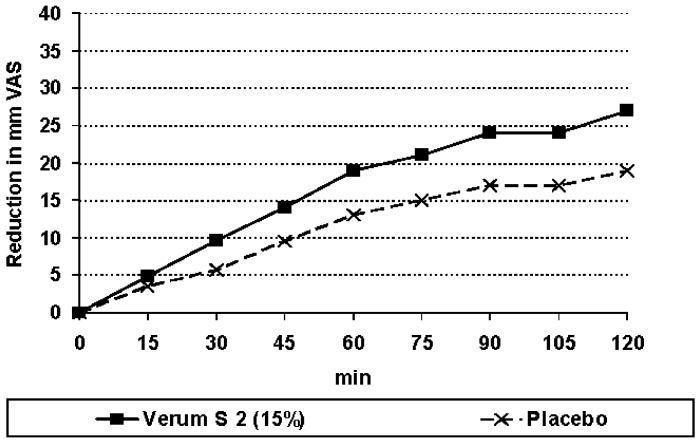

Fig. 2. The p-value following comparison of the AUCs of PID versus placebo is as follows (study part 2): Verum S2 (15 m/m) vs. placebo 0.0021. The mean baseline VAS value for verum was 67.4 mm, for placebo 63,7 mm.

EFFICACY

Primary efficacy variables

Figs. 1 (part 1) and 2 (part 2) show the mean PID values (PP collective 1st study part) over 2 hours after the first application (VAS reduction in mm).

The study was continued with Verum S2 (15 % m/m; p-value of 0.093 was within the predefined range of 0.00365 – 0.3).

In order to test whether the Verum S2 is statistically significant at the 2.5 % level, the p-values of part 1 and

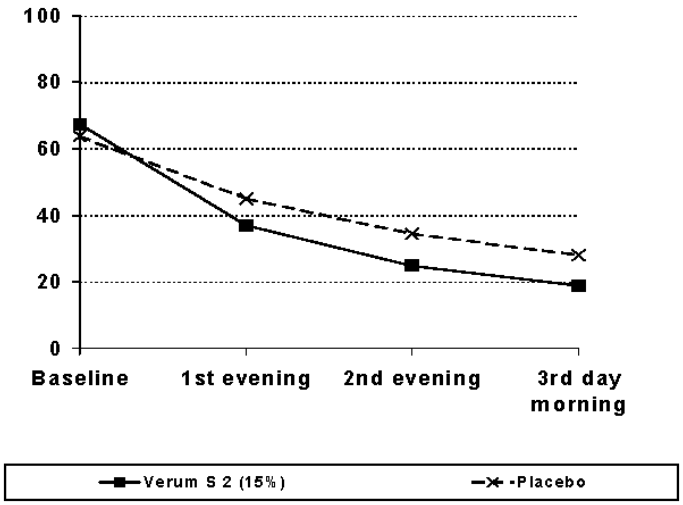

Fig.3. Change of pain intensity difference during study treatment.

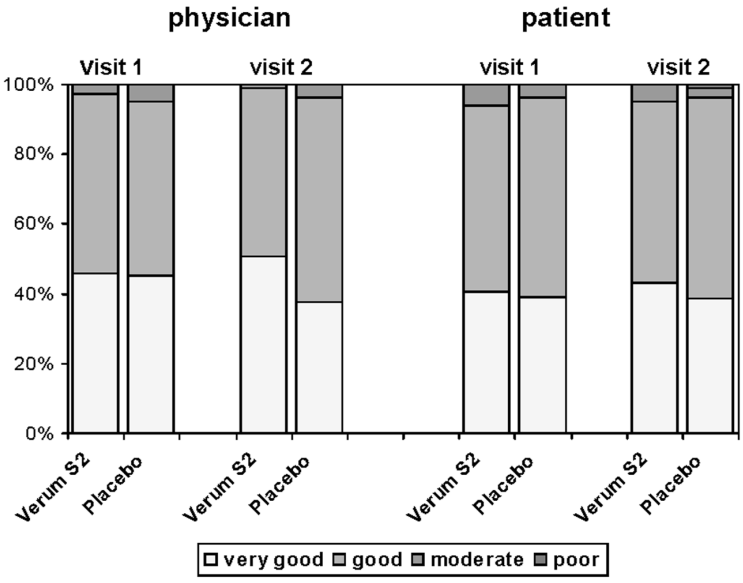

Fig.4. Assessment of the tolerability by the physicians and patients (main study).

part 2 for Verum S2 (15 % m/m) had to be multiplied: 0.093 x 0.0021 = 0.0001953 is clearly lower than the predefined critical value of 0.001062. Hence, the confirmatory analysis showed a statistically significant therapeutic superiority of Verum S2 over placebo.

Secondary Efficacy Variables

Meaningful pain relief and time to complete pain reduction CPR):

No statistically significant difference with regard to meaningful pain relief was observed. In the 1st study part 1 patient in the placebo group, 3 patients in the 30% group and 8 patients in the 5% group reached a CPR within the first two hours after study treatment. In contrast, in the 2nd study part a CPR within the first 2 hours after first application of study treatment was only reached for very few patients (n = 3 patients in the Verum S2 15 % m/m group, n = 1 patient in the placebo group, study part 2).

Fig. 3 shows the change of PID during study treatment (PP collective, part 2).

Already in study part 1 a highly significant ($p < 0.001$) time effect was seen over the study period with regard to all therapy groups, but there was no difference between the study groups themselves. However, a significant effect on pain reduction ($p < 0.0001$) was seen for both treatment (in favour of verum S2) and time.

Early Treatment Discontinuations

Altogether, n=5 early treatment discontinuations (n=1 in study part 1, n=4 in study part 2) were seen during the whole study: 3 patients in the placebo group (lack of compliance, lack of efficacy, 2 AEs with fever and exsudative lymphadenitis), 2 patients in the verum groups (30 %: 1 AE – tonsillitis; 15 % - lack of efficacy).

Safety and Tolerability

In study part 1, 6 AEs in n = 5 patients (1 placebo group, 2 verum S1, 2 verum S3) were reported:

- one report of tonsillits in n=1 patient (patient on verum S1):
  severe intensity, *no causal relationship* to study medication, treatment discontinuation
- two AE reports in n=2 patients:
  dry pharynx (pat. no. 26, placebo) and burning of mild intensity (patient on verum S2): causal relationship to study medication *probable*
- three AE reports in n=2 patients:
  moderate cough attack and mild headache (both events in a patient on verum S1), mild itching in the throat (patient on verum S3): causal relationship to study medication *possible*, treatment was continued

In the main study, 2 AEs in n=1 patient (placebo group) were reported:

- (patient on placebo) fever of 39∞C and exsudative lymphadenitis with exsudations were reported, no causal relationship to study medication, treatment discontinuation

No serious AEs were reported.

Overall Safety and Tolerability Assessment by the Physicians and the Patients

The overall safety assessment was „good“ or „very good“ in over 90 % by either the physicians or the patients. There were no significant differences in the safety assessment between the physician or the patient. In study part 2, only ca. 1 % of the patients assessed the tolerability of the placebo as „poor“ on visit 2.

Figure 4 compares the physician's and patient's tolerability assessments of both study visits.

Discussion

To our knowledge the present study is the first randomised, placebo-controlled trial which was conducted to demonstrate efficacy and tolerability of a herbal medicinal product as a pharyngeal spray in the indication acute pharyngitis (sore throat). We were not aware of any guidelines in the field of pharyngitis studies or any trials with herbal preparations similar to ours. Therefore, because little information for such a trial was available it was designed as a randomised, double-blind, placebo-controlled, multicentre, parallel group trial with an *adaptive design* and an *interim analysis*. The primary endpoint was the change of throat pain intensity (spontaneous pain, not pain on swallowing; see placebo discussion below) documented every 15 min within the first 2 hours after the first application as compared to baseline using the 100 mm Visual Analog Scale (= VAS): the Area Under the Curve (AUC) of the Pain Intensity Differences (PID) was assessed.

Adult patients of both sexes from 18 years with the key symptom acute spontaneous throat pain independent from swallowing (duration less that 48 hours, at least 40 mm on a VAS 100 mm) were included thus being representative for the claimed indication.

The efficacy analysis convincingly demonstrated that the spray (equivalent to verum S2 15 % m/m) was significantly superior in throat pain reduction within the first 2 hours after the first application ($p = 0.0001953$). Regarding the secondary endpoints MPR and complete throat pain reduction within the first 2 hours after the first application, no significant superiority could be shown: this may be due to the fact that acute pharyngitis is a very painful condition in which a 50 % or even complete pain reduction may not be achieved without a local anesthetic component. However, a ca. 44 % pain reduction within 2 hours following the first application was found for verum S2 15 % m/m in both study parts compared to a ca. 34 % pain reduction in the placebo group (see also below).

Since the placebo contained the same amount of alcohol as the Verum S2 15 % m/m the clinically relevant difference can be contributed to the sage fluid extract itself. The clinically relevant superiority is well in line with the positive efficacy assessment of both physician and patient ($p < 0.0012$ and $p < 0.012$, resp.). In addition, if the pain intensity reduction is regarded of the whole study duration, there is a significant difference in favor of the verum S2 15 % m/m vs. placebo ($p < 0.0001$).

However, some findings have to be discussed because they seem to be not in consistence with the results regarding the primary efficacy parameter. In the 1st study part it was not possible to show a dose dependency of the sage spray. One theoretical explanation might be the fact that the sage extract is a complex active ingredient. One cannot exclude that in higher concentrations some components might have an inverse effect on the efficacy. In other words, a dose-response linearity as it is well known for many chemically defined drugs may not be present for herbal preparations. This hypothesis is at least in part supported by Derendorf and Butterweck (2004) who – though in another context – stated that a quantitative relationship between concentrations and effects is not (necessarily) linear so that doubling or bisecting of the concentration may lead to only minor changes of the observed effects.

One issue to discuss is the observation that the magnitude of the mean pain reduction (in mm on the VAS) of the verum S2 15 % in the 2nd study part is about 27 mm and therefore in the similar range as the placebo effect in the 1st study part. At first, “pain” is a very subjective parameter and consequently “pain studies” are challenging with regard to their interpretation. One reason for this difference between the two study parts might be that the two collectives are different to some extent. However, regardless wether study part one or study part two is considered the difference between verum S2 15 % and placebo is within 11 to 12 mm. We think that this is a relevant finding because it is constantly seen over the study and reflects the “real” effect of the verum which we think is clinically relevant.

Another phenomenon is the placebo effect itself. In the indication acute pharyngitis a placebo arm is a very high challenge because such simple measurements as drinking cold water or avoiding swallowing already may have some beneficial effects on pain relief. Therefore, spontaneous pain was chosen for the primary efficacy parameter and not pain on swallowing because the swallowing technique itself again may influence the

pain feeling. The considerations around a "true" placebo in this indication may be reflected somehow by the relatively high "placebo effect" of ca. 34 % within this study. Last but not least, pharyngitis is known to have a relatively high spontaneous remission rate (see also below).

Some secondary parameters do not seem to be consistent with the result of the primary one. One example is the number of patients reaching a meaningful pain relief (MPR) of 50% or a complete pain relief (CPR) within the first 2 hours. For MPR it might be that a pain reduction of at least 50 % may be too high a hurdle for a mild herbal drug. Such a response to drug treatment may only be achieved with chemical drugs and / or local anesthetics. The same may be valid for CPR. Another explanation could be the number of patients which might be not high enough to detect a possible small difference. Again, though not obvious at first glance, a high spontaneous healing rate and / or a heterogenity in the patient groups may account for these open issues.

With regard to the safety analysis no serious adverse events occured. The AEs reported were of mild or moderate severity. A causal relationship – assessed as possible or probable to study medication – was made for 5 AEs: dry pharynx and burning, a cough attack, headache, and itching of the throat. The other 3 AE reports (tonsillitis, fever, and exsudative lymphadenitis), which occurred in 2 patients who were withdrawn from the study, were not considered related to study medication. These findings are more in line with the course of the pharyngitis itsself, in particular in more severe cases with possible bacterial superinfection. However, it is not reported whether bacterial superinfection was the possible reason for the 2 „deteriorations". The excellent tolerability of the verum S2 15 % m/m is reflected in the positive assessment both of the physician and the patient: more than 90 % of the physicians and the patients assessed the tolerabitliy to be „good" or „very good".

Five patients discontinued the study treatment early. However, the number as well as the reasons for early study termination are well within a normal range of clinical studies and do not point to a relevant lack of efficacy or a relevant safety problem. Because of the excellent tolerability of the spray as demonstrated within the study no major or serious side effects during the short term use of Sidroga Salvia Rachenspray should be expected in daily clinical practice. Altogether we do not think that due to the mild effect of the sage extract any serious condition will be masked by the use of the spray.

Of course, there are already alternatives available on the market for the treatment of acute pharyngitis. Buccal tablets containing local anaesthetics, substances out of the NSAID group (ibuprofen, flurbiprofen etc.) or even drinking a cold glass of water can lead to a significant pain relief. Considering NSAIDs, poor tolerability in certain patients even for short duration limits the use of these drugs. A glass of clean cold water may not be available at any time through daily life. In general, treatment with mild effective herbal drugs is wanted by many patients. Thus, the sage spray tested in this study may combine mild efficacy, excellent tolerability and easy and comfortable use in particular – but not limited to - for patients in working life.

In summary, the study convincingly demonstrated the clinical efficacy of the spray (containing 15 % of a sage fluid extract [1:1]) in the symptomatic pain management of acute pharyngitis with a very beneficial safety profile not requiring major application restrictions. It could be an excellent starting treatment for acute sore throat before going to other alternatives includings antibiotics or analgesics.

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