ORIGINAL ARTICLE

EPS 7630 IS EFFECTIVE IN CHILDREN WITH ACUTE, NON-β-HAEMOLYTIC STREPTOCOCCAL TONSILLOPHARYNGITIS RESULTS OF A DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTRE TRIAL

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Abstract

Objective: After positive clinical study results of EPs 7630 in children with acute bronchitis, the present study was conducted to confirm its efficacy in the treatment of acute tonsillopharyngitis (ATP). Methods: Children aged 6 to 10 years presenting with ATP, negative for β-haemolytic streptococcus and without mandatory indication for antibiotic treatment were included. Duration of treatment was 6 days. The trial was conducted as a double-blind, placebo-controlled, multicentre study. Results: The analysis comprising data from 78 randomised patients showed success rates of 90.0% in the EPs 7630 and 44.7% in the placebo group (p<0.001). Furthermore, the analysis indicated highly significant advantages of EPs 7630 (n=40) over placebo (n=38) regarding all signs and symptoms typical of ATP, e.g. for the total score of objective and subjective symptoms on days 2, 4 and 6 (p<0.001). Conclusion: EPs 7630 is effective in treating children with ATP and is very well tolerated.

Keywords: EPs 7630, Umckaloabo, Pelargonium sidoides, Placebo, Tonsillopharyngitis

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Introduction

Sore throat continues to be one of the most frequent reasons for children, adolescents and young adults to consult a physician. The vast majority of these patients presents with an acute infection which is mostly caused by viruses and only to a lesser degree by bacteria [1]. Accordingly, investigations in the past years have shown fewer than 20% of patients to have a clear indication for treatment with antibiotics, i.e. a positive test for β-haemolytic streptococci [2]. Not only because of the low incidence of indisputable indications for antibiotics, but also because rheumatic fever has become very rare in the western world, the indiscriminate prescription of...
antibiotics has increasingly come under criticism [3-5]. This criticism is additionally supported by the American Academy of Pediatrics which recommends antibiotic therapy only for children with pharyngitis confirmed to be caused by group A Streptococci [6]. The need for alternative treatments of sore throat is therefore particularly obvious in patients without a definite indication for antibiotic therapy, i.e. those patients for whom the result of a rapid test for β-haemolytic streptococci is negative.

EPs 7630*, a herbal drug preparation from the roots of Pelargonium sidoides, has been shown to exhibit antiviral, antibacterial, immunomodulatory and secretomotor properties [7-13]. A series of placebo-controlled clinical trials have been published, showing the efficacy and tolerability of EPs 7630 in adults and children with acute bronchitis [14-19], adults with common cold [20] and acute rhinosinusitis [21]. Efficacy and long-term tolerability of EPs 7630 was also shown, as an add-on therapy, in the treatment of patients suffering from chronic obstructive pulmonary disease, leading to a significant prolongation of time to first acute exacerbation and reduction in both exacerbation frequency and antibiotic use [22]. A first double-blind randomized placebo-controlled study investigating EPs 7630 in children with acute non-group-A beta-haemolytic Streptococcus (GABHS) tonsillopharyngitis has been published in 2003 [23]. In this formerly published study, a 6-day treatment with 20 drops of EPs 7630 tid was shown to significantly reduce the severity of symptoms. The aim of the present study in children with acute GABHS-negative tonsillopharyngitis was to investigate the efficacy and safety of EPs 7630 when administered in a different dosage regimen during the first two treatment days.

Methods

Design. The present trial was designed as a randomized, double-blind, placebo-controlled, multicentre study with two parallel groups. To enable an early stopping of the trial in case of a significant result or sample size recalculation, a group sequential design allowing for interim analysis under control of the significance level was chosen [24].

Patients. Inclusion criteria were: children 6 to 10 years of age with signs and symptoms of acute tonsillopharyngitis (ATP); duration of complaints ≤48 hours; negative dip-and-react test for β-haemolytic streptococci; total score of tonsillopharyngitis-specific objective and subjective symptoms ≥6 and written informed consent by parents or legal guardians. Exclusion criteria were: angina lacunaris, angina follicularis; mandatory indication for antibiotic treatment (e.g. abscess, tonsillogenic sepsis); intake of any other medication which could impair the study results; condition after rheumatic fever, glomerulonephritis following a streptococcal infection, chorea minor Sydenham; increased tendency to bleed (e.g. concomitant treatment with coumarin-derivatives), severe cardiac, renal, hepatic diseases or immunosuppression; known or suspected hypersensitivity to study medication; concomitant medication that might impair the study results (e.g. antibiotics); participation in another clinical trial during the past 3 months; patients or guardians with impaired legal competence and unable to understand the nature, relevance and consequences of the trial.

*EPs® 7630 is the active ingredient of the product Umckaloabo® (ISO-Arzneimittel, Ettlingen, Germany).
**Conduct and ethics.** The trial was conducted in six trial sites in Kiev, Ukraine and performed according to the ICH-GCP guidelines and the Declaration of Helsinki. The study protocol and declaration of consent were reviewed and approved by the local Ethics Committee and the Competent Authority prior to the start of the study. Written informed consent by the parents or legal guardians was in place for all patients. A Data Monitoring Board reviewed the evaluation of the interim analysis and made the final decision on continuation or termination of the trial.

**Study medication and assessments.** Duration of treatment according to study protocol was 6 days. This treatment duration had been shown to be appropriate for efficacy investigation of the study medication in a previous study reported by Blochin and Heger [25]. All patients fulfilling all inclusion and none of the exclusion criteria at the admission visit (Day 0) were randomized to receive either EPs 7630 or a matched placebo. EPs 7630 is a herbal drug preparation from the roots of *Pelargonium sidoides* (1:8-10; extraction solvent: ethanol 11%, w/w). Patients were instructed to take 20 drops of study medication hourly on the first 2 days while awake and thereafter 20 drops three times per day for a further 4 days. Follow-up assessments were scheduled for Day 2, Day 4 and Day 6. Drug intake was also checked on Day 2, Day 4 and Day 6. Compliance was ensured by checking the amount of returned trial medication. Blinding was achieved by using placebo solution with identical appearance as the EPs 7630 solution. Study medication for an individual patient was labelled with a random number and the investigator was unaware of the randomization schedule.

The primary endpoint to assess the efficacy of EPs 7630 compared to placebo was the proportion of responders after 4 days of treatment (success of therapy). Response was defined as a total score of ≤4 points with regard to tonsillopharyngitis-specific objective and subjective symptoms. These symptoms consisted of dysphagia, sore throat, salivation, reddening, coating left, coating right as well as fever and were evaluated by the study physicians. The first six symptoms were assessed by the categories “severe” (3), “moderate” (2), “mild” (1) and “no symptom” (0). Fever was classified as ≤37.5°C = 0; 37.5°C – <38.5°C = 1; 38.5°C – <39.5°C = 2; >39.5°C = 3. Thus a maximum total score of objective/subjective symptoms of 21 points was possible.

In addition, the following symptoms were classified by the study physicians: swelling of pharynx, uvula, tonsils and lymph nodes; pain on pressure on lymph nodes; pain in the limbs; headache. The same categories as described above were used for assessment, but no total value was calculated. Furthermore, medical history, concomitant medication and adverse events reported in the course of the trial were documented. At study end (day 6), a further dip-and-react test for β-haemolytic streptococci was performed.

**Statistics.** The success criterion based on response to therapy was used for hypothesis testing. All other analyses were performed descriptively.

For sample size calculation, such a success of therapy was expected to be seen in about 70% of patients taking EPs 7630, but only about 45% of the placebo patients, as based on the results of a pilot study. Under these assumptions and selection of an α-error of 0.05 and a β-error of 0.20, this resulted in an average number of 39 patients per treatment group in a triangular sequential design [24]. Success rates were analyzed with Fisher’s exact test. As a matter of principle, the last observation was carried forward (LOCF) for analysis in case of missing data. To
examine any influence of the LOCF method on results [26], the data were additionally analyzed with recent methods for the handling of missing values [27,28].

In the following the mean and standard deviation are given unless otherwise stated. All data are presented based on the intention-to-treat (ITT) collective. Additional per-protocol (PP) analyses were conducted as prespecified in the study protocol.

Results

Interim analysis. The interim analysis conducted after inclusion of 44 patients (EPs 7630: 24, placebo: 20) showed significant superiority of EPs 7630 over placebo with a success rate of therapy of 87.5% in the EPs 7630 group versus 40.0% in the placebo group (p=0.0014, Fisher’s exact test).

The criterion to stop the study was thus formally fulfilled, but the study was continued until the average planned number of 78 patients was reached in order to guarantee a sufficient number of patients evaluable for secondary target parameters. Accordingly, the data of 78 patients went into the final analysis (EPs 7630: 40, placebo: 38). Since all 78 patients had been randomised, received study medication and provided data on efficacy and tolerability, they could be considered for the ITT analysis.

Demographic and anamnestic data. A total of 56.4% of study participants were male, the mean age of all participants was 8 ± 1 years (Mean ± SD). Average height was 127 ± 9 cm and weight on average 27 ± 6 kg. Patient history showed an ENT infection in 87.2% of participants, namely acute rhinopharyngitis in 70.5% and angina tonsillaris in 64.1%. Both treatment groups were comparable regarding demographic data and symptoms; e.g. the total score of objective and subjective symptoms was 8.7 ± 1.5 in the EPs 7630 group and 8.8 ± 1.6 in the placebo group (p=0.849, Wilcoxon test). All patients had a negative test for β-haemolytic streptococci at the start as well as at the end of the study.

Course of the study. The numbers and reasons for discontinuations throughout the study as well as the exclusion from analysis groups are shown in Figure 1.
Figure 1. Study discontinuation and exclusion from analysis groups. ITT

Randomized (n=78)

Allocated to EPs 7630 on Day 0 (n=40)
- Received EPs 7630 (n=40)

Continued to Day 2 (n=39)
- Discontinued intervention due to withdrawal of informed consent (n=1)

Continued to Day 4 (n=36)
- Discontinued intervention due to withdrawal of informed consent (n=1), worsening symptoms/insufficient efficacy (n=1) and adverse event (n=1)

Continued to Day 6 (n=32)
- Discontinued intervention due to withdrawal of informed consent (n=1), worsening symptoms/insufficient efficacy (n=1) and adverse event (n=1) and unknown reasons (n=1)

Allocated to placebo on Day 0 (n=38)
- Received placebo (n=38)

Continued to Day 2 (n=38)
- No discontinuation

Continued to Day 4 (n=27)
- Discontinued intervention due to withdrawal of informed consent (n=3), worsening symptoms/insufficient efficacy (n=6), adverse event (n=1) and other reasons (n=2)

Continued to Day 6 (n=9)
- Discontinued intervention due to worsening symptoms/insufficient efficacy (n=13), adverse event (n=3) and unknown reasons (n=2)

Analysis

Analyzed for safety (n=40)
- No exclusion from ITT analysis

Included in ITT analysis (n=40)
- Excluded from PP analysis due to major protocol violations: withdrawal of informed consent (n=2) and discontinuation because of adverse event (n=2)

Included in PP analysis (n=36)

Analyzed for safety (n=38)
- No exclusion from ITT analysis

Included in ITT analysis (n=38)
- Excluded from PP analysis due to major protocol violations: withdrawal of informed consent (n=3), discontinuation because of adverse event (n=1), insufficient compliance (n=1) and discontinuation because patient relocated (n=1)

Included in PP analysis (n=32)
Efficacy. In the final analysis the rate of patients with successful therapy (total score of objective/subjective symptoms ≤4 points at Day 4) was 90.0% in the EPs 7630 group versus 44.7% in the placebo group (p<0.001, Fisher’s exact test), corresponding to a number needed to treat (NNT) of 2.21.

The change of the total score over the course of the study also revealed a clear superiority of EPs 7630 over placebo on Day 2, Day 4 and Day 6 (p<0.001, Wilcoxon test; Figure 2).

Figure 2. Total scores of objective and subjective symptoms over time. Mean 95% CI, LOCF. The total score of the objective and subjective symptoms could range from 21 (maximum intensity) to 0 (remission). A significant difference between the groups was seen on Day 4, and a relevant difference was discernible as early as Day 2 (p<0.001, p-value of Wilcoxon test).
Analysis of the individual symptoms at Day 4 consistently showed distinctly better results in the patients treated with EPs 7630 compared to placebo, namely concerning above all the symptoms sore throat, reddening, swelling of the tonsils, fever, pain on pressure on lymph node, headache, swelling of the uvula and swelling of the pharynx (Figure 3).

**Figure 3. Improvement of symptoms.** The length of the light grey bar corresponds to the percentage of patients with "symptom resolved" and that of the dark grey bar to the percentage with "symptom improved" on Day 4. The percentages are based on the number of patients who had the respective symptom on Day 0. Significant differences were seen between the EPs 7630 group and the placebo group with respect to remission and improvement of symptoms by Day 4 (*p<0.02, p-value of Fisher’s exact test).

Additional consumption of paracetamol was allowed to combat fever ≥38.5°C and was documented in 35.0% of patients in the EPs 7630 group versus 47.4% in the placebo group (p=0.358, Fisher’s exact test).

Evaluation of patients’ diaries indicated an onset of improvement in 75.0% of patients treated with EPs 7630 within the first 4 days after start of therapy (Figure 4). Merely 15.8% of patients in the placebo group observed an equivalent improvement in the same time interval.

The results of the PP analysis confirmed those of the ITT population (data not shown).
Figure 4. Time to onset of improvement. As reported in patients’ diaries, ITT (p<0.001, p-value of Wilcoxon test).
Safety and tolerability. In total, 17 adverse events in 16 patients (9 AEs in 8 patients in the EPs 7630 group and 8 AEs in 8 patients in the placebo group) were documented (Table 1). All AEs were trivial infections or rather superinfections or symptoms of the same. A causal relationship of AEs was considered as unlikely with regard to study medication in two patients in the EPs 7630 group; all other AEs were assessed as unrelated to study medication. Serious adverse events did not occur.

Table 1. Patients with adverse events. The low level term according to MedDRA 14.0 is given, in order of incidence in the placebo group

<table>
<thead>
<tr>
<th></th>
<th>EPs 7630</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Randomised = ITT</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td>Patients with adverse events</td>
<td>8</td>
<td>8</td>
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<tr>
<td>Upper respiratory tract infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Gastrointestinal discomfort</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Tracheitis</td>
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<td>0</td>
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<tr>
<td>Scarlet fever</td>
<td>1</td>
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<tr>
<td>Rubella</td>
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<td>Rhinitis</td>
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<td>Common cold</td>
<td>1</td>
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<tr>
<td>Dry cough</td>
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This impression is also confirmed by global assessment of tolerability by the patients, revealing no significant difference (p-Wert=0.181, Wilcoxon test) between the two treatments (Figure 5).

Figure 5. Patients’ assessment of tolerability. *ITT.*
Discussion

The results of the present trial show that ATP not requiring antibiotics can be promptly and successfully (NNT = 2.21) treated with EPs 7630. Efficacy of EPs 7630 was shown to a similar degree in all signs and symptoms of the disease. This is especially true for the symptoms sore throat and headache: those symptoms which are generally perceived as a particular strain by the patients.

The rapidly achieved onset of improvement in patients treated with EPs 7630 is of major relevance.

A distinct and clinically relevant difference to the placebo group was revealed in a pronounced improvement of symptoms under EPs 7630 as early as 2 to 3 days after start of treatment. The plausibility of the results is underlined by comparable improvements under placebo in similar groups of patients as reported in the literature [29].

The results are also in accordance with previously published data from another clinical trial with EPs 7630 in children with acute GABHS-negative tonsillopharyngitis [23]. In this formerly published trial, patients took 20 drops of EPs 7630 or placebo tid for a treatment duration of 6 consecutive days. In the present, similarly designed pilot study in children with acute GABHS-negative tonsillopharyngitis, EPs 7630 was administered in a dosage regimen that consisted of an application of 20 drops of the study medication hourly during the first two treatment days and 20 drops tid from day 3 through day 6. Both studies showed comparable efficacy and safety results. In addition, the results of the present trial add to the favourable safety profile of EPs 7630 as they underline the good safety and tolerability of an intake of more than 20 drops EPs 7630 tid.

As to the treatment of patients with sore throat, there currently seems to be a great discrepancy on an international level between evidence-based medicine [30,31] or rather the corresponding guidelines [32,33] on the one hand and the actual therapy regimen of the attending physicians on the other hand [34-36]. Although there is already a trend towards conservative antibiotic treatment, more exact diagnostics excluding β-haemolytic or group-A streptococci should yield further improvements [37]. A regimen of diagnosis and treatment involving preceding detection of β-haemolytic streptococci and, only then, prescription of antibiotics actually proved to be more cost-effective than six other strategies including therapeutic nihilism and direct prescription of antibiotics [38]. A further analysis revealed a combination of a clinical scoring system and a rapid antigen test to be the most cost-effective strategy in diagnosing and treating sore throat in children [39]. These findings further show that the design of the present trial with a prior test for β-haemolytic streptococci conforms to guidelines and is practicable as well.

In the current guidelines symptomatic treatment is intended as a therapeutic alternative for patients with sore throat who have no clear indication for antibiotic treatment. This seems obvious in case of a purely viral infection and may also explain the lack of placebo-controlled trials in patients tested negative for β-haemolytic streptococci. In fact evidence-based recommendations exist for very few symptomatic therapies. Exceptions to this are chlorhexidine/benzydamine [40] and the analgesic paracetamol and ibuprofen [41]. At any rate it may be questioned whether simple sore throat justifies such a far-reaching intervention. In contrast, EPs 7630 has clear benefits since it so far has shown clinically relevant efficacy as well.
as excellent tolerability, as in the present study.

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