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Research Article

Efficacy and safety of chlorhexidine-lidocaine vs. placebo in adult patients with acute pharyngitis.

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Abstract

Acute pharyngitis is characterized by sore throat accompanied by inflammation and burning sensation in the throat causing impaired swallowing and, in some cases, impaired saliva production. The present randomized, double-blind, placebo-controlled phase III study was conducted to compare the efficacy and safety of a lemon-flavored lozenge formulation (Medica®) containing a combination 5 mg chlorhexidine (dihydrochloride) with 1 mg lidocaine (hydrochloride).

After bacterial infection was ruled out using the McIsaac score and completion of a Rapid Antigen Strep Test (RAST), 209 patients were randomized. The study was conducted in six centers located in Denmark, France and Georgia, and consisted of: a 2-h stationary phase followed by a 4-day ambulatory phase. Patients were allowed to take up to a maximum of 10 lozenges per day. Throat pain and dysphagia were assessed on visual analogue scales (VAS) and therapeutic response was evaluated in terms of reduction in Tonsillopharyngitis Severity Score (TSS). Pain relief and quality of life were also evaluated, as was product safety.

Combined chlorhexidine and lidocaine was found to be superior to placebo regarding several of the parameters investigated, particularly sore throat and erythema. During the ambulatory phase, the significance level was reached for sore throat improve-

ment, Tonsillopharyngitis Severity Score and pain attenuation. No severe adverse events were observed. Safety was considered very good or good in 99% of patients.

The chlorhexidine-lidocaine combination demonstrated higher efficacy than placebo regarding several measured parameters, which exhibited significant improvement from the stationary phase (sore throat at 120') through to the follow-up visit at day 4 (sore throat and erythema). This combination was thus shown to provide symptomatic relief of sore throat as well as reducing signs of inflammation such as erythema. The combination lozenge was very well tolerated and is considered very safe. It may be offered as a first-line treatment for acute pharyngitis.

Trial registration:

EU Clinical Trial Register number: 2013-005521-23

Keywords:

Clinical trial; sore throat; pharyngitis; chlorhexidine; lidocaine

Abbreviations:

URTI: Upper Respiratory Tract Infections

GAS: Group A Beta-Hemolytic Streptococcus

OTC: Over The Counter

e-CRF: Electronic Case Report Form

CRA: Clinical Research Associate

GCP: Good Clinical Practice

ENT: Ear, Nose And Throat

RST: Rapid Strep Test

TSS: Tonsillopharyngitis Severity Score

VAS: Visual Analogue Scale

AE: Adverse Event

SAE: Severe Adverse Event

AUC: Area Under Curve

FAS: Full Analysis Set

ITT: Intent To Treat

PP: Per Protocol

Introduction

Sore throat is considered the predominant symptom in upper respiratory tract infections (URTI). These infections, which are of bacterial or viral origin, are manifested by inflammatory signs of the pharynx and/or tonsils. Patients consult a physician chiefly for pain and dysphagia [1]. It has been estimated that 50-95% of sore throats in adults are caused by respiratory virus infection [2-4]. Online consumer surveys, completed by 6465 respondents who experienced throat discomfort in the previous 12 months, showed that patients considered common cold/influenza to be responsible for their throat discomfort in 72% of cases [4].

The majority of patients (80%) present with a viral infection, usually with adenovirus, influenza virus, respiratory syncytial virus, para-influenza virus or a coxsackie virus [5-8]. These patients receive only symptomatic therapy for pain [8].

Ten to 15% of infections are caused by group A beta-hemolytic streptococcus (GAS), and antibiotic therapy may be needed due to potential complications [2, 9]. Other bacteria such as Mycoplasma, Chlamydia, *Arcanobacterium Haemolyticum, Corynebacterium Diphtheriae*, groups C and G Streptococci, and certain anaerobes can also be involved in sore throat, but in practice they play a minor role [7].

In the symptomatic treatment of non-bacterial sore throat, two categories of medicinal products are used: antiseptics and local anesthetics. Antiseptics prevent infectious complications by destroying the bacteria present superficially in the mouth. In the test product, we used chlorhexidine on account of its bactericidal and bacteriostatic effects [10]; in addition, it has demonstrated *in vitro* anti-viral effects, mainly on enveloped viruses such as H1N1 influenza virus [11]. Chlorhexidine is often used as an antiseptic in mouth washes and sprays, for example in post-radiation mucositis. The foregoing studies militate in favor of an anti-inflammatory effect of chlorhexidine compared to other anti-inflammatory active substances [12, 13]. A local analgesic agent such as lidocaine reduces or removes pain. Lidocaine is an intermediate-acting local anesthetic belonging to the class of alpha amino acid amides (amide type). The targets of local anesthetic drugs such as lidocaine are voltage-gated sodium channels, which are dynamic transmembrane proteins found in excitable cells (e.g. neurons, cardiomyocytes, and skeletal muscle cells) that open and close for ion conduction [14-18]. Lidocaine has a rapid onset of action and anesthesia is obtained within a few minutes [19, 20]. As well as its very potent effect, lidocaine has also demonstrated good tolerability [21]. It is considered very safe, especially compared to ester-type local anesthetics such as benzocaine [22-24]. Moreover, in addition to this anesthetic property, a potent antimicrobial effect has been described for topical lidocaine solutions [25].

Several products are available both on prescription and over the counter (OTC), in spray or lozenge forms [26-29]. Lozenges are one of the most widely used solid dosage forms. This formulation extends the time of drug contact within the oral cavity, thereby eliciting a specific effect [30].

Randomized studies have been conducted on the treatment of non-bacterial pharyngitis and/or sore throat in order to evaluate their efficacy and safety. Published trials have assessed the efficacy of amylmetacresol and 2,4-dichlorobenzyl alcohol or AMC/DCBA (Strepsil®) vs. placebo [27, 28, 31, 32], of Echinacea/sage vs. chlorhexidine/lidocaine [29], of ambroxol [33, 34], of benzocaine [35], and of lidocaine [21].

Prior to the current study, a multicenter randomized pilot study was conducted in 40 patients (Q4 2013) to select the evaluation criteria and determine the variability thereof. This study enabled determination of the requisite number of patients and of the primary endpoint for the present trial [36].

The object of the trial was to demonstrate the superiority of lozenges containing combined chlorhexidine hydrochloride/lidocaine hydrochloride vs. placebo in the management of sore throat due to non-bacterial pharyngitis.

Methods

Study design

This was an international, multicenter, randomized, double blind, parallel group, placebo-controlled study. The study comprised a stationary phase, in which assessment was done in the investigators' medical office up to 2 hours after the first dose, and an ambulatory phase, during which assessment was made by the patient using a diary over four days. At day four, a follow-up visit was done as well as a phone call at day 7 to check any adverse events. The study was conducted between 17 February 2014 and 27 April 2015. Study data were collected by investigators via an electronic case report form (e-CRF Quanta View® 4.2) and monitored by a clinical research associate (CRA) in accordance with GCP recommendations.

Study population

Patients were recruited by an ear, nose & throat (ENT) specialist in Køge (Denmark), a general practitioner in Paris (France), and ENT specialists at four investigational centers in Tbilisi (Georgia). The study was registered (EudraCT number 2013-005521-23) and approved by the relevant ethical committees (Danish Health and Medicines Authority, French National Drug Safety Agency and the Ministry of Labor, Health and Social Affairs of Georgia). The study was carried out in accordance with the ethical requirements of the Declaration of Helsinki.

Inclusion criteria were age >18 years; acute non-bacterial pharyngitis or an erythematous viral sore throat within 72 hours before the inclusion date, absence of bacterial infection (McIsaac score < 2 and Rapid Strep test (RST) negative), Tonsillopharyngitis Severity Score (TSS) ≥ 5, and provision of written informed consent.

Non-inclusion criteria included the presence of peritonsillar or retro-pharyngeal abscess, pseudomembranous pharyngitis, other causes of dysphagia or pharyngitis, and pregnancy or lactation. Non-inclusion criteria relating to treatment comprised: use of oral or local steroidal or non-steroidal anti-inflammatory drugs, of analgesic or anesthetic agents during the 48 hours prior to enrolment, or of antibiotic therapy during the 14 days before the inclusion date.

Stationary phase

After signature of the informed consent and checking of all inclusion and non-inclusion criteria, the investigator made baseline measurements, then allocated treatment in order of randomization and asked the patient to take the first lozenge.

Baseline measurements assessed by the investigator consisted mainly of (i) the Tonsillopharyngitis Severity Score (TSS), and (ii) sore throat and dysphagia scores on a visual analogue scale (VAS).

The TSS score is composed of independently evaluated parameters: sore throat, dysphagia, secretions and erythema. All parameters were measured on a scale of 0 to 3 (0=absent, 1 = mild, 2 = moderate, 3 = severe). The sum of these scores forms the overall TSS score.

Sore throat and dysphagia were measured by VAS at baseline then at 10 minutes, 30 minutes, 60 minutes and 120 minutes after the initial drug intake.

Ambulatory phase

At the end of the first visit, patients were given a self-assessment diary as well as the investigation treatment units. The diary comprised seven questions to be answered by the patient each day. The investigator asked the patient to complete one diary for each day. Patient were to record the frequency of daily administration, as well as their symptoms of sore throat and dysphagia, and to evaluate quality-of-life activities. The activities evaluated consisted of swallowing, drinking, eating, talking, reading and sleeping. All parameters were evaluated on a scale of 0 to 4 (0 = not limited; 1 = slightly limited; 2 = fairly limited; 3 = very limited; 4 = impossible). The patients' answers enabled a total quality-of-life score to be calculated.

At day 4, the investigator collected the self-evaluation diary as well as the unused investigational drug. He assessed the TSS score then evaluated sore throat and dysphagia using the VAS

strip. He checked protocol compliance as regards intake of any concomitant treatment and performed counting of all unused lozenges.

At day seven, a phone call was made during which the investigator checked whether any adverse events (AE) had occurred since the last visit.

Treatment and blinding

Randomization was achieved by means of computer-produced randomization (SAS® software) of study treatments, with subsequent distribution to patients following allocation of a unique number in numerical sequence. Patients were randomly allocated to one of two groups. Randomization was balanced by blocks of 4 treatment units: 2 units of the investigational medication and 2 units of placebo. Patient allocation was carried out at each center consecutively in ascending order of treatment numbers.

A box of 40 lozenges was given to each patient. In each box, four blister strips were prepared, each containing 10 lozenges comprising either chlorhexidine dihydrochloride 5 mg and lidocaine hydrochloride 1 mg (excipients : sorbitol, magnesium stearate, aspartame, lemon flavoring, acesulfame K) (Medica®) or a placebo made up of all the drug excipients.

Patients were instructed to take one lozenge as needed, up to a maximum of 10 lozenges per day, and to begin a new blister strip each day.

Compliance was checked by the investigator during the follow-up visit by counting the number of lozenges used from each blister strip.

Efficacy Endpoints

The efficacy endpoints for the study were as follows:

area under the change-over-baseline curve (AUC) for throat soreness and dysphagia from 0 to 2 hours.

change over baseline in sore throat relief (on a 7-point scale) at 120 minutes after the first dose;

comparison between the two groups from day 1 to day 4 for change in VAS score for sore throat and dysphagia;

comparison of therapeutic response (reduction at D4 by 50% vs. baseline TSS score) between the two groups;

quality-of-life score (total score by adding up each 4-point score for the following parameters: soreness, swallowing, talking, sleeping, eating, reading, speaking) noted in the patients' self-assessment questionnaires.

Safety endpoints

The safety endpoints were the evaluation by the investigator of overall product acceptability and the absence of severe adverse events.

Statistical analysis

A sample population of 176 patients (88 patients per group) was deemed necessary to detect a relative difference of +44% in mean AUC of severity of throat soreness from 0 to 120 minutes between the two treatment groups based on the results of a previous pilot study; assuming a 15% rate of non-assessable patients, a total of 202 patients was needed in order to ensure the inclusion of at least 176 patients in the final analysis.

The statistical analysis was performed using SAS® 9.4 software (SAS Institute Inc., Cary, USA). The efficacy analysis was performed on the full analysis set (FAS) population, i.e. all patients enrolled. An additional consistency analysis was performed on the per-protocol (PP) population (i.e. all patients in the ITT population not presenting a major protocol deviation) and the ITT population. The safety population was defined as all patients randomized and receiving at least one treatment.

Regarding quantitative criteria, baseline and final values and change at endpoint were described using standard error on the mean, quartiles, minimum and maximum values and 95% CI for the mean. Regarding qualitative criteria, the frequency and percentage of each modality were presented.

Gaussian quantitative variables were analyzed using parametric analysis of covariance (ANCOVA). The differences between the investigational drug and placebo were determined using the mean square error from the ANCOVA analysis and using Fisher's protected Least Square Difference method. For validating the model, the normality of data distribution was checked using a Shapiro-Wilk test on the residual. Where normality was not verified ($p<0.10$), transformation of the AUC or a non-parametric ANCOVA were performed.

Questions involving numeric ordinal scales were analyzed with Repeated Measures ANCOVA. Questions having binary answers were analyzed using a logistic regression model.

Adverse events were based on the safety population. Adverse events (AE) were coded using MedDRA version 15.0. The safety analysis includes tabulation of the type and frequency of all adverse events. Results were summarized in terms of their relationship to the studied drugs and by severity (i.e. mild, moderate or severe). Differences between groups in numbers of patients reporting treatment-emergent adverse events and assessment of acceptability of products and of local tolerance by the investigator were compared via chi-squared or Fisher's exact test in the event of insufficient sample size.

All tests were two-sided and used a significance level of 0.05.

Results

Patient disposition

Of the 210 included patients, 205 completed the entire study. One patient was not randomized for failure to meet the inclusion criteria and 4 patients withdrew prematurely (Figure 1).

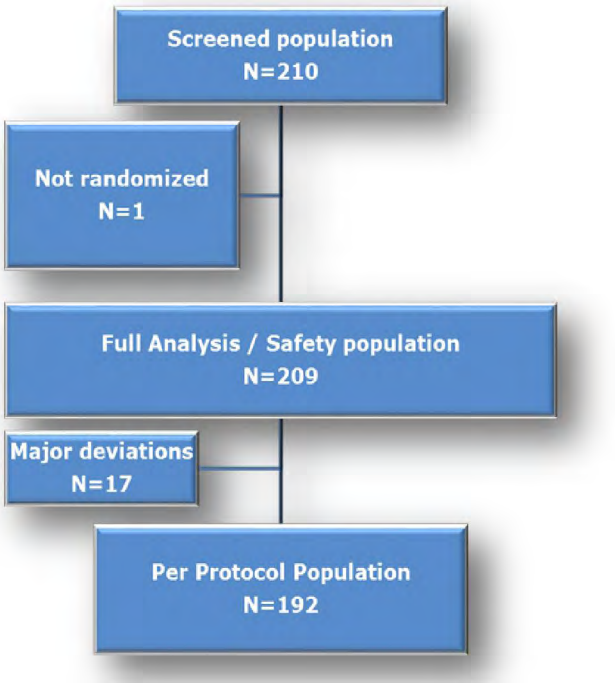

Figure 1. Data set flow chart.

None of the treatments was unblinded. Only 2 randomization errors were identified. During the blind review, 17 patients were considered to exhibit major deviations due to intake of prohibited concomitant treatments.

The FAS population thus comprised 209 patients and the per protocol population 192 patients (91.9%).

Non-compliance with the study schedule between enrolment visit V1 (D1) and follow-up visit V2 (D4) was observed for only one (1) patient and was considered a major deviation.

Missing or incomplete evaluation of efficacy criteria was observed for 4 patients. However, these patients were analyzed in the per protocol population using the Last Observation Carried Forward method.

Patient demographics

The mean age of the study populations was 38.8 ± 13.4 years: respectively 38.0 ± 14.4 years in the active treatment group and 39.7 ± 12.3 years in the placebo group. The sex ratio (male/female) was 0.45: respectively 0.34 in the active treatment group and 0.58 in the placebo group (Table 1).

PARAMETER		CHR-LIDO (n=106)	PLACEBO (n=103)
Sex	Men	27 (25.5%)	38 (36.9%)
	Women	79 (74.5%)	65 (63.1%)
Age (years)	Mean ±SD	38.0±14.4	39.7±12.3
	Median	34.7	38.9
	95%CI	35.2 / 40.7	37.3 / 42.1
Time interval : onset pharyngitis - enrolment	Mean ±SD	2.4±0.5	2.5±0.6
	Median	2.0	2.0
Sore throat (VAS)	Mean±SD	61.7±15.5	62.5±14.1
Dysphagia (VAS)	Mean ±SD	53.6±18.3	52.9±18.5

Table 1. Baseline demographic characteristics in the two treatment groups (FAS population) CHR-LIDO: treatment group, PLACEBO: placebo group, SD : standard deviation

There was no statistical difference between the two groups regarding past medical and surgical history (42.5% in the active treatment group vs. 44.7 in the placebo group), concomitant diseases (36.8% in each group) or previous treatments (2.8% in each group).

Treatment intake

All blister strips were returned after use and the remaining lozenges counted.

The mean treatment duration was significantly lower in the active treatment group than in the placebo group (3.5 ± 0.7 days vs. 3.7 ± 0.5 days; p<0.002) as was the total number of lozenges used over the 4-day period (18.1 ± 7.8 vs. 21.0 ± 7.9; p<0.01).

The number of lozenges used was significantly lower in the active treatment group (Figure 2).

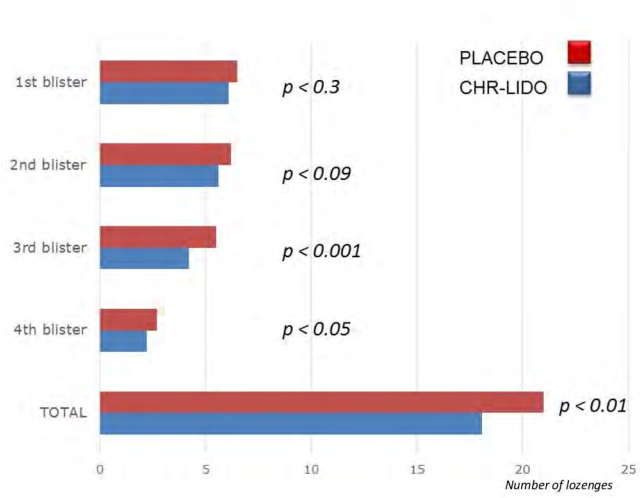

Figure 2. Daily number of lozenges intake (mean value) from day 1 to day 4.

Efficacy results

All efficacy results are shown for the full analysis population. There was in fact almost no difference in results between the analyzed populations. The active treatment group showed superiority in all efficacy evaluations, with either significant or nearly significant results.

VAS evaluation of sore throat

At baseline, the mean VAS score for sore throat was 61.7 ± 15.5 in the active treatment group vs. 62.5 ± 14.1 in the placebo group.

After 120 minutes, throat soreness significantly improved in the active treatment group vs. the placebo group (42.4 ± 20.8 vs. 48.5 ± 17.2), as did the mean change over baseline (19.3 ± 20.0 vs. 14.0 ± 16.8; p<0.05) (Figure 3).

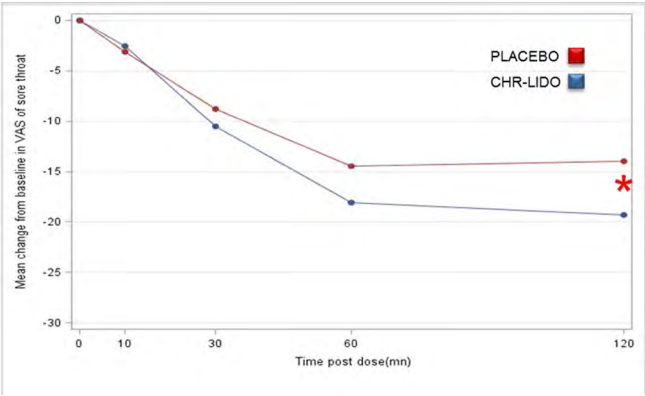

Figure 3. Sore throat – Visual Analogue Scale Mean changes from baseline to 120' (* significant p =0.05)

The AUC for change over baseline between 0 and 120 minutes showed improvement close to significance in the active treatment group vs. placebo (1694.6 ± 1867.5 vs. 1339.7 ± 1660.3; p=0.09).

The mean AUC for change over baseline between D1 and D4 was significantly improved in the active treatment group compared to the placebo group (92.0 ± 60.8 vs. 74.4 ± 84.6; p=0.04).

At D4, mean change over baseline showed significant improvement in the active treatment group vs. placebo (51.4 ± 21.0 vs. 44.0 ± 23.1; p<0.002).

VAS evaluation of dysphagia

At baseline, the mean VAS score for dysphagia was 53.6 ± 18.3 in the active treatment group vs. 52.9 ± 18.5 in the placebo group.

There was no significant difference between the active treatment group vs. the placebo group (34.2 ± 21.4 vs. 37.7 ± 19.3), either after 120 minutes or in terms of mean change over baseline (19.1 ± 21.8 vs. 15.1 ± 18.3).

The AUC of change over baseline between 10 and 120 minutes showed no significant improvement in the active treatment group vs. placebo (1816.9 ± 2200.3 vs. 1452.8 ± 1885.7).

The mean AUC for change over baseline between D1 and D4 was almost significantly improved in the active treatment group compared to the placebo group (89.8 ± 63.0 vs. 70.8 ± 79.9; p=0.08).

At D4, mean change over baseline showed significant improvement in the active treatment group vs. the placebo group (46.5 ± 21.8 vs. 40.9 ± 23.7; p=0.05).

Tonsillopharyngitis Severity Score (TSS)

At baseline, distribution was not significantly different between the two groups for overall score or for any component of TSS.

The mean change in total TSS score between baseline and D4 demonstrated a significant improvement in the active treatment group compared to the placebo group (5.4 ± 2.3 vs. 4.4 ± 2.5; p<0.002).

The mean change in sore throat between baseline and D4 showed significant improvement in the active treatment group vs. the placebo group (1.7 ± 0.8 vs. 1.4 ± 0.8; p<0.001) as evidenced by dysphagia (1.7 ± 0.7 vs. 1.4 ± 0.9; p<0.02) and erythema (1.6 ± 0.9 vs. 1.2 ± 0.9; p<0.001) (Figure 4). There was no difference regarding secretions.

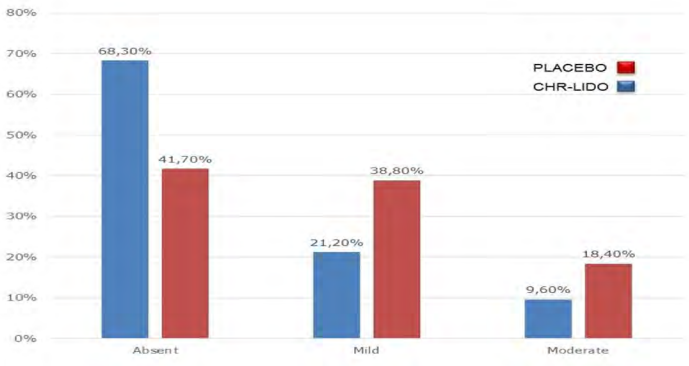

Figure 4. TSS - Evaluation of Throat erythema at day 4.

Pain attenuation

Pain attenuation was evaluated at day 1, 120 minutes after administration of the first dose of study drug. The active treatment significantly reduced pain compared to the placebo; 53.9% of patients presented moderate or total pain attenuation in the active treatment group vs. 35.6% in the placebo group (p<0.01) (Figure 5).

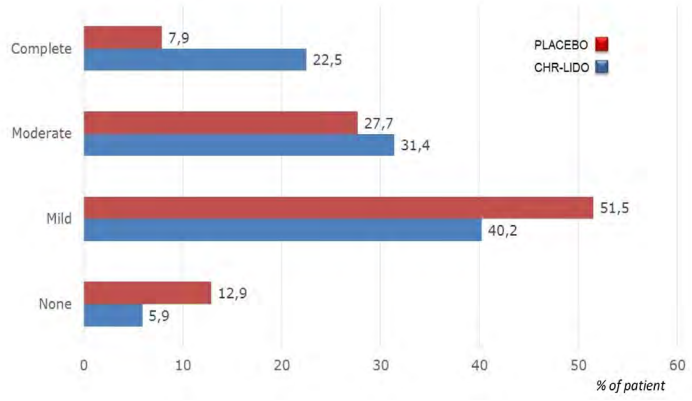

Figure 5. Pain attenuation at 120' (% of patient p<0.01)

Quality of life

The mean of change over baseline in total score (figure 6) showed significant superiority in the active treatment group vs. placebo at D2 (2.4 ± 2.2 vs. 1.9 ± 2.0, p=0.01), D3 (4.8 ± 3.1 vs. 4.2 ± 2.9, p<0.02) and D4 (6.2 ± 3.6 vs. 5.5 ± 3.7, p<0.005). At day 4, all quality-of-life parameters evaluated exhibited improvement (p<0.05).

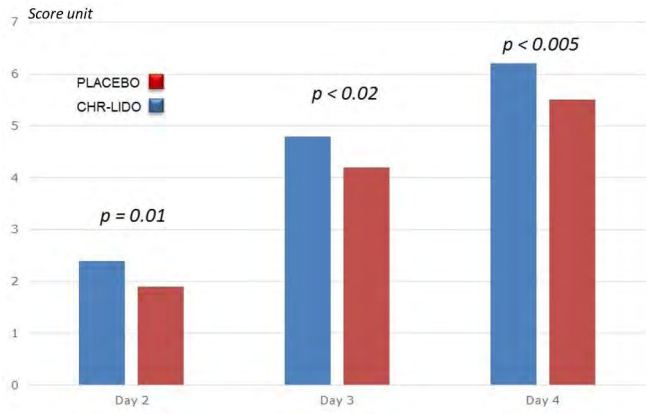

Figure 6. Total score improvement of quality of life Mean change of the total score D2, D3 and D4 compared to baseline.

Safety results

No serious adverse events (SAE) were reported during the study. Of the 209 treated patients, 33 (15.8%) reported at least one adverse event suspected to be related to the investigational product, i.e. 17 (16.2%) in the active treatment group and 16 (15.4%) in the placebo group, but without any statistically significant differences between the groups.

Discussion

Only very few comparative controlled trials have been carried out on non-bacterial sore throat using a combination of two different locally delivered active substances [28, 29]. Most such trials concern local substances used alone: anesthetics such as lidocaine [21], ambroxol [33, 34], benzocaine [35], combined antiseptics [27, 32] or the procyanidin fraction of tannin [37, pilot study].

Lidocaine, a well-established local anesthetic, is characterized by rapid onset of action and intermediate duration of effect. It has been previously shown to relieve symptoms of acute pharyngitis when delivered in a lozenge format [21]. As well as anesthetic properties, a potent antimicrobial effect has been described for topical lidocaine solutions [25]. Chlorhexidine has been used and well investigated as a disinfectant in a broad range of applications [10, 11]. It is considered the drug of choice for disinfection and is used in mouthwashes after surgery [38]. The combination of these two substances in the treatment of sore throat represents a new therapeutic combination and the present article is the first measuring the efficacy and safety thereof.

This trial was conducted in a population in which the possibility of Group A streptococcus (GAS) pharyngitis was ruled out by clinical McIsaac score [39-41] and by a Rapid Antigen Strep Test [42, 43, 44]. The efficacy evaluation parameters were based on validated scores and criteria: visual analogue scales (VAS) [29, 27, 35, 28] and TSS score [29, 45, 46]. The clinical trial was constructed using information drawn from the previous pilot study [36] and was of international design. Since a combination of chlorhexidine and lidocaine was being investigated, the study was designed to determine the efficacy of the treatment with regard to both pain attenuation and anti-inflammatory effects.

In the present study, all efficacy results showed superiority of the chlorhexidine-lidocaine combination vs. placebo. Pain was evaluated using visual analogue scales and the results reached significance at 2 hours (pain attenuation, p<0.01), remaining significant thereafter until the final evaluation at day 4: mean AUC D1-D4 for sore throat (p=0.04) and mean change over baseline at D4 for dysphagia (p=0.05).

In order to investigate the anti-inflammatory effect, a scoring system was adapted from the literature [45]. Mean change in TSS was significantly improved between baseline and D4 (p<0.002). Among the parameters used in TSS, erythema (an objective parameter showing evidence of inflammation) significantly improved after 4 days (p<0.001). This anti-inflammatory effect could undoubtedly be brought closer to the antiviral activity of chlorhexidine, which has already been demonstrated in an *in vitro* test [11].

In general, the mean change in total quality-of-life score was also significantly improved at D2, D3 and D4.

The majority of publications in the literature are limited to investigation a few hours after a single administration of the

product, despite the establishment by a cohort study in young adults that the mean duration of acute viral URTI is between 5 and 6 days [47]. Thus, the results observed after the second hour as well as at D2, D3 and D4 are of particular significance. This is emphasized by the reduced number of lozenges taken, which was already significantly lower at D2 in the treatment group vs. placebo, and by the shorter duration of treatment in the active treatment group.

Overall, we can conclude that the improvement of symptoms of acute viral URTI (sore throat and erythema) proves that this combination confers not only symptomatic relief of sore throat, but also an anti-inflammatory effect, as shown by the reduction of erythema.

The active treatment was equally tolerated as the placebo. Safety as assessed by the investigator was either very good or good. The observed adverse events were mild or moderate, of short duration (median = 1.0 days) and regressed readily without sequelae and without premature study discontinuation compared to 5 randomized trials of a local anesthetic, ambroxol [34], which resulted in 1% premature discontinuation due to AEs.

The safety of lidocaine has already been demonstrated in several publications. Mogensen et al. 2012 investigated lidocaine 100-mg lozenges in order to suppress gag reflex before intubation. Even at a concentration of up to 100 mg, no adverse events were reported [48]. Moreover, as a result of similarity in packaging, 198 notifications of accidental intake of chlorhexidine/lidocaine combination in children were received by 2 anti-poison centers in Australia. There have been 28 cases with complete follow-up in which the product was given through therapeutic error. The mean ingested doses were 2.7 mg/kg for lidocaine was (standard deviation: 1.3 mg) and 0.06 mg/kg for chlorhexidine (standard deviation: 0.03 mg). The highest ingested dose of lidocaine was 5.9 mg/kg. Two children developed only minor symptoms. No other adverse events were reported in the other 26 cases [49]. These results show that even in very small children, combined chlorhexidine/lidocaine has only very limited side effects. The concentrations used in the latter study were higher than the concentration used in the lozenges studied in the current trial. Moreover, the liquid was swallowed directly, whereas the presently studied lozenges are for topical use on mucous membrane.

Overall, it may be concluded that the decision to use lidocaine in the present product compared to benzocaine or ambroxol can be considered a very safe choice since benzocaine belongs to the ester-type local anesthetic group known for its adverse events [22-24], while ambroxol is currently under review by the European Medicines Agency due to an increased number of reports concerning allergic reactions [50]. While the most common adverse effects of chlorhexidine are allergic reactions and hypersensitivity, they are reported only very rarely [51]. In the present study, no serious allergic reactions were reported, which is confirmed by an animal study (guinea pigs) in which chlorhexidine was classified as a very weak sensitizer [52].

Conclusion

Lozenges containing a combination of chlorhexidine (5 mg) and lidocaine (1 mg) demonstrated higher efficacy than placebo with regard to several of the measured parameters, particularly erythema and sore throat. These parameters showed significant improvement from the stationary phase (sore throat) through to the day 4 visit (sore throat and erythema), which represents the duration of an actual viral infection. This proves that this combination lozenge not only provides symptomatic relief of sore throat but also shows anti-inflammatory effects such as erythema reduction. The combination lozenge was very well tolerated and is considered very safe, and it may therefore be proposed as a first-line treatment for acute pharyngitis.

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Authors' contributions

The trial was designed and carried out by an independent contract research organization, Quanta Medical SA, Rueil-Malmaison, France. The Data Management and statistical services of Quanta Medical provided the randomization list and performed the statistical analysis. Othar Zourabichvili reviewed the final data and the study report. The final manuscript was reviewed and approved by all authors.

Competing interests

Marc Van Diest is head of the medical department & Kris De Ceulaer is research scientist of Qualiphar NV (Bornem, Belgium) which sponsored the clinical trial. They were not involved in the clinical trial course. All other authors have no competing interests.

References

1. Van Driel ML, De Sutter A, Deveugele M, Peersman W, Butler CC et al. Are sore throat patients who hope for antibiotics actually asking for pain relief? Ann Fam Med. 2006, 4(6): 494-499.

2. Summers A. Sore Throats. Accid Emerg Nurs. 2005,13: 15-17.

3. Worral GJ. Acute Sore Throat. Can Fam Physician. 2007, 53(11): 1961-1962.

4. Addey D, Shephard A. Incidence, causes, severity and treatment of throat discomfort: a four-region online questionnaire survey. BMC Ear Nose Throat Disord. 2012: 12:9.

5. Esposito S, Blasi F, Bosis S, Droghetti R, Faelli N et al. Aetiology of acute pharyngitis: the role of atypical bacteria. J Med Microbiol. 2004, 53(7): 645-651.

6. Vincent MT, Celestin N, Hussain AN. Pharyngitis. Am Fam Physician. 2004, 69(6): 1465-1470.

7. Bisno A.L. Acute pharyngitis. N Engl J Med. Vol. 2001, 344: 205-211.

8. Wessels MR. Streptococcal pharyngitis. N Engl J Med. 2011, 364: 648-655.

9. Matthys J, De Meyere M, van Driel ML, De Sutter A. Differences among international pharyngitis guidelines: not just academic. Ann Fam Med. 2007, 5(5): 436-443.

10. Moshrefi A. Chlorhexidine. J West Soc Periodontol Abstr. 2002, 50(1): 5-9.

11. Michel C, Salvatico S, Belkhelfa H, Haddioui L, Roques C. Activity of Drill® lozenges on the main microorganisms responsible for upper respiratory tract infections. Eur Ann Otorhinolaryngol Head Neck Dis. 2013, 130(4): 189-193.

12. Nicolatou-Galitis O. Systematic review of anti-inflammatory agents for the management of oral mucositis in cancer patients. Support Care Cancer 2013, 21(11): 3179-3189.

13. Cheng KF, Ka Tsui Yuen J. A pilot study of chlorhexidine and benzydamine oral rinses for the prevention and treatment of irradiation mucositis in patients with head and neck cancer. Cancer Nurs. 2006, 29(5): 423-430.

14. Brunton L, Chabner B, Knollman B. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 12th Edition. McGraw-Hill, 2011.

15. Fozzard HA, Sheets MF, Hanck DA. The sodium channel as a target for local anesthetic drugs. Front Pharmacol. 2011, 2: 68.

16. Lidocaine (Accession Number: DB00281 (APRD00479, DB05291)). DrugBank, 2015.

17. Parfitt K. Sweetman SC. Martindale: The complete drug reference. 32nd ed. London : Pharmaceutical Press.1999, 49(6): 613.

18. Buchholz V, Leuwer M, Ahrens J et al. Topical antiseptics for the treatment of sore throat block voltage-gated neuronal sodium channels in a local anaesthetic-like manner. Naunyn Schmiedebergs Archiv Pharmacol. 2009, 380: 161-168.

19. Daubländer M, Roth W, Kleeman PP. Clinical investigation of potency and onset of different lidocaine sprays for topical anesthesia in dentistry. Anesth Pain Control Dent. 1992, 1(1): 25-28.

20. Schønemann NK, van der Burght M, Arendt-Nielsen L, Bjerring P. Onset and duration of hypoalgesia of lidocaine spray applied to oral mucosa--a dose response study. Acta Anaesthesiol Scand. 1992, 36(7): 733-735.

21. Wonnemann M, Helm I, Stauss-Grabo M, Röttger-Luer P, Tran C-T et al. Lidocaine 8 mg sore throat lozenges in the treatment of acute pharyngitis. A new therapeutic option investigated in comparison to placebo treatment. Arzneimittelforschung. 2007, 57(11): 689-697.

22. Chowdhary S, Bukoye B, Bhansali AM, Carbo AR, Adra M et al. Risk of topical anesthetic-induced methemoglobinemia: a 10-year retrospective case-control study. JAMA Intern Med. 2013, 173(9): 771-776.

23. U.S. Food and Drug Administration (FDA). FDA Drug Safety Communication: FDA continues to receive reports of a rare, but serious and potentially fatal adverse effect with the use of benzocaine sprays for medicinal procedures. 2011.

24. Hartman NR, Mao JJ, Zhou H, Boyne MT, Wasserman AM et al. More methemoglobin is produced by benzocaine treatment than lidocaine treatment in human in vitro systems. Regul Toxicol Pharmacol. 2014, 70(1): 182-188.

25. Pelz K, Wiedmann-Al-Ahmad M, Bogdan Ch, Otten JE. Analysis of the antimicrobial activity of local anaesthetics used for dental analgesia. Journal of Medical Microbiology. 2008, 57(1): 88-94.

26. McNally D, Simpson M, Morris C, Shephard A, Goulder M. Rapid relief of acute sore throat with AMC/DCBA throat lozenges: randomised controlled trial. Int J Clin Pract. 2010, 64(2): 194-207.

27. Wade AG, Morris C, Shephard A, Crawford GM, Goulder MA. A multicentre, randomised, double-blind, single-dose study assessing the efficacy of AMC/DCBA Warm lozenge or AMC/DCBA Cool lozenge in the relief of acute sore throat. Bmc Fam Pr. 2011, 12: 6.

28. McNally D, Shephard A, Field E. Randomised, double-blind, placebo-controlled study of a single dose of an amylmetacresol/2,4-dichlorobenzyl alcohol plus lidocaine lozenge or a hexylresorcinol lozenge for the treatment of acute sore throat due to upper respiratory tract infection. J Pharm Pharm Sci. 2012,15(2): 281-294.

29. Schapowal A, Berger D, Klein P, Suter A. Echinacea/sage or chlorhexidine/lidocaine for treating acute sore throats: a ran-

domized double-blind trial. Eur J Med Res. 2009, 14(9): 406-412.

30. Majekodunmi S.O. A review on lozenges. Am. J. Medecine Medical Sciences. 2015, 5(2): 99-104.

31. Gupta D, Agrawal S, Sharma JP. Evaluation of preoperative Strepsils lozenges on incidence of postextubation cough and sore throat in smokers undergoing anesthesia with endotracheal intubation. Saudi J Anaesth.. 2014, 8(2): 244-248.

32. McNally D, Simpson M, Morris C, Shephard A, Goulder M. Rapid relief of acute sore throat with AMC/DCBA throat lozenges: randomised controlled trial. Int J Clin Pract. 2010, 64(2): 194-207.

33. Chenot JF. Efficacy of Ambroxol lozenges for pharyngitis: a meta-analysis. BMC Family Practice. 2014, 15(1): 45.

34. de Mey C, Peil H, Kölsch S, Bubeck J, Vix JM. Arzneimittel-Forschung (Drug Research). Efficacy and safety of ambroxol lozenges in the treatment of acute uncomplicated sore throat. EBM-based clinical documentation. 2008, 58(11): 557-568.

35. Chrubasik S, Beime B, Magora F. Efficacy of a benzocaine lozenge in the treatment of uncomplicated sore throat. Eur Arch Otorhinolaryngol. 2012, 269(2): 571-577.

36. Medica® pilot study 2013 (unpublished)

37. Shrivastava R. A Pilot Clinical Trial to Evaluate the Efficacy of a Topical Antiviral Osmotically Active Hypertonic Solution for the Treatment of Influenza Virus Induced Sore Throat. J Clinic Trials. 2011, 1:13.

38. Sharma SK, Kaur J. Randomized Control Trial on Efficacy of Chlorhexidine Mouth Care in Prevention of Ventilator Associated Pneumonia (VAP). Nursing and Midwifery Research Journal. 2012, 8: 169-178.

39. McIsaac WJ, White D, Tannenbaum D, Low DE. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. CMAJ. 1998, 158(1):75-83.

40. Fine AM, Nizet V, Mandl KD. Large-Scale Validation of the Centor and McIsaac Scores to Predict Group A Streptococcal Pharyngitis Arch Intern Med. 2012, 172(11): 847-852.

41. McIsaac WJ, Kellner JD, Aufricht P, Vanjaka A, Low DE. Empirical validation of guidelines for the management of pharyngitis in children and adults. JAMA. 2004, 291(13): 1587-1595.

42. Stewart EH, Davis B, Clemans-Taylor BL, Littenberg B, Estrada CA et al. Rapid Antigen Group A Streptococcus Test to Diagnose Pharyngitis: A Systematic Review and Meta-Analysis. PLoS One. 2014, 9(11): e111727.

43. Chan JYC, F Yau, F Cheng, D Chan, B Chan et al. Practice Recommendation for the Management of Acute Pharyngitis. HK J Paediatr (new series). 2015, 20: 156-162.

44. Gerber MA, Shulman ST. Rapid diagnosis of pharyngitis caused by group A streptococci. Clin Microbiol Rev. 2004, 17: 571-580.

45. Bereznoy VV, Riley DS, Wassmer G, Heger M. Efficacy of extract of Pelargonium sidoides in children with acute non-group A beta-hemolytic streptococcus tonsillopharyngitis: a randomized, double-blind, placebo-controlled trial. Altern Ther Health Med. 2003, 9(5): 68-79.

46. Schachtel BP, Fillingim JM, Beiter DJ, Lane AZC, Schwartz LA. Subjective and objective features of sore throat. Arch Inter Méd. 1984, 144(3): 447-500.

47. Lindbaek M, Francis N, Cannings-John R, Butler CC, Hjortdahl P: Clinical course of suspected viral sore throat in young adults: cohort study. Scand J Prim Health Care. 2006, 24(2): 93-97.

48. Mogensen S, Treldal C, Feldager E et al. New lidocaine lozenge as topical anesthesia compared to lidocaine viscous oral solution before upper gastrointestinal endoscopy. Local Reg Anesth. 2012, 5: 17-22.

49. Balit CR, Lynch AM, Gilmore SP, Murray L, Isbister GK. Lignocaine and chlorhexidine toxicity in children resulting from mouth paint ingestion: a bottling problem. J Paediatr Child Health. 2006, 42(6): 350-353.

50. European Medicines Agency (EMA). Start of review of ambroxol and bromhexine. EMA/203011/2014. 2014.

51. Krautheim AB, Jermann TH, Bircher AJ. Chlorhexidine anaphylaxis: case report and review of the literature. Contact Dermatitis. 2004, 50(3): 113-116.

52. Goh CL. Contact sensitivity to topical antimicrobials. (II). Sensitizing potentials of some topical antimicrobials. Contact Dermatitis. 1989, 21(3): 166-171.