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Role of biclotymol-based products in the treatment of infectious sore throat

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Abstract. – OBJECTIVE: In clinical practice, physicians often prescribe antibiotics for the treatment of sore throat. However, current guidelines clarify that antibiotics should not be used in patients with less severe presentation of this condition in order to relieve symptoms. With the aim to limit the onset of resistance and reduce the occurrence of adverse events, other remedies can be used instead. For the past forty years, the use of biclotymol-based products has been a common practice for the treatment of sore throat. This paper reviews and critically discusses the role of biclotymol-based products as a local treatment of infectious oropharyngel diseases.

MATERIALS AND METHODS: Papers for consideration for the present article were retrieved in Authors' personal collection of literature. In order to extend the number of considered papers, a PubMed search was also conducted. Papers were selected for inclusion according to their relevance for the topic, as judged by the Authors.

RESULTS: Biclotymol is a molecule characterized by a marked antibacterial efficacy, also associated with evident anti-inflammatory and analgesic action demonstrated in a number of preclinical studies. Noteworthy, all these actions have a fast onset of effect and are long-lasting. Two well-conducted investigations have assessed biclotymol in spray formulation. Notably, both studies proved its efficacy, with the wide majority of patients reporting "very good" or "good" efficacy. The analgesic and anti-inflammatory properties of biclotymol were also demonstrated. Tolerability was excellent.

CONCLUSIONS: Enough evidence exists to recommend the use of biclotymol as a prompt, effective and safe first-line option for the treatment of sore throat.

Key Words:
Biclotymol, Antibiotics, Infectious oropharyngeal diseases.

Introduction

The diagnosis and treatment of acute sore throat have been extensively discussed by the recent guidelines issued by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID)[1]. In many cases, sore throat is of viral origin, but bacterial etiology is reported as well. In more details, Group A streptococcal remains the most common bacterial cause of acute pharyngitis[2]. Noteworthy, antibiotic therapy should be prescribed only to patients with proven Group A streptococcal infection. At present, there is a major need to encourage physicians to prescribe alternative treatments; antibiotics should be reserved for patients at increased risk of complications[3].

An ideal treatment for sore throat should provide the symptomatic relief that patients seek and, at the same time, treat the underlying cause of this condition, using locally-delivered formats such as lozenges and sprays. For the past forty years, the use of biclotymol-based products has been a common practice for the treatment of sore throat.

This paper reviews and critically discusses the role of biclotymol-based products as a local treatment of infectious oropharyngeal diseases.

Selection of Evidence

Papers for consideration for the present article were retrieved in Authors' personal collection of literature. In order to extend the number of considered papers, a PubMed search was also conducted using different combinations of pertinent keywords (e.g. biclotymol AND sore throat), without any limitations in terms of publication date and language. Papers were selected for inclusion according to their relevance for the topic, as judged by the Authors.

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Biclotymol: an Overview of Chemical Properties

Biclotymol [2,2-methylenebis(4-chloro-3-methyl-isopropylphenol); chemical abstract service number 15686-33-6] is a thymol derivative belonging to the class of bisphenols (Figure 1). It is characterized by antiseptic action, and it was first described in 1967[4,5]. Its molecular formula is $C_{21}H_{26}Cl_2O_2$ and the molecular weight is 381.3 Da.

Biclotymol presents as a white to white off-white powder. It is practically insoluble in water, freely soluble in ethanol (96%), chloroform and ether. The melting point of biclotymol is 126-130°C.

Anti-microbial Activity

Biclotymol has a multiple spectrum of actions: namely, it has bacteriostatic, bactericidal, anti-inflammatory and analgesic activity. Therefore, it may be used as a first-line option for the relief of sore throat, as a local treatment of oropharyngeal diseases to be used since the onset of symptoms.

In more details, the antibacterial effect of different biclotymol concentrations on opportunistic microorganisms, which constitute the more frequent infectious pathogens of lower and upper respiratory tract, has been demonstrated *in vitro*[5]. This action is due to a direct action on constitutive mucopolysaccharides, which disrupts bacterial walls[6,7]. Noteworthy, biclotymol is able to adhere to the proteins expressed in oropharyngeal mucosa. Therefore, they act as a drug reservoir, prolonging the antibacterial action of bioclotymol[6].

German-Fattal showed the bacteriostatic activity of biclotymol from the dosage of 1 µg/ml against most bacterial strains such as *S. aureus*, *Enterobactericae*, *Pseudomonas spp*, *Hemophilus spp*[7]. More recently, Katosova et al[4] showed that biclotymol 20 mg/mL exerts an immediate bactericidal effect (exposure < 1 min). At lower concentrations, a dose-dependent antibacterial effect was observed[4]. The rapid antibacterial effect of biclotymol was confirmed in a subsequent study from the same group, which demonstrated that the bactericidal activity of this drug is primarily directed against Gram-positive cocci[5]. Table I shows the minimal inhibitory concentration (MIC) and the amount (absolute and %) of colony forming units (CFU) of survived bacteria at various concentrations against different bacterial strains[5]. *Streptococcus pneumoniae* and *Haemophilus influenzae* were the most sensitive pathogens to biclotymol exposure (MIC values of 0.15 mg/mL)[5].

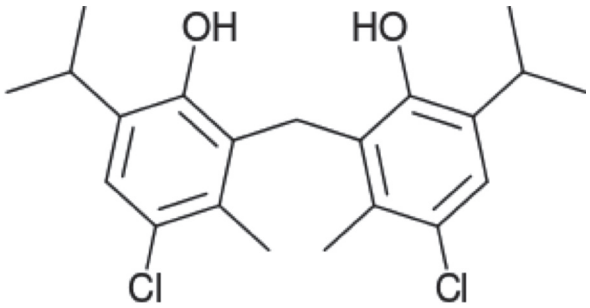

Figure 1. Chemical structure of biclotymol.

Recent findings showed that the 5-minute application of a 90% biclotymol-based mouthwash (Hexaspray, biclotymol 2.5%, Laboratoires Bouchara Recordati, France) reduced by 5-log the concentration of *Pseudomonas aeruginosa* strains (data on file). Similar results were reported for *Escherichia coli* and *Enterococcus* strains (data on file). In particular, the antibacterial properties of the biclotymol-based mouthwash have been tested according to the norms NF-EN 1040 on different bacterial strains, namely *Pseudomonas aeruginosa*, *Staphylococcus aureus* (two mandatory strains for this antibacterial test), *Escherichia coli* and *Enterococcus hirae* (additional strains). The antimicrobial activity was tested at different times (5, 15, 30 and 60 minutes) and different concentrations (10%, 75% and 90% v/v) at a temperature of 35°C. The antibacterial efficacy started at 75% dilution for the two mandatory strains. Of note, it was evident (5 log) at 90% concentration even on the additional species *E. hirae*, recognized as particularly resistant to antiseptics and representative of the bacteria in the *Streptococcus* genus, responsible for the wide majority of non-viral cases of pharyngitis.

Moreover, in the same study the antifungal effect of biclotymol against *Candida albicans* species was tested at different times (30, 60, 90 and 120 minutes) and concentrations (10%, 75% and 90%) (data on file). A non-negligible level of activity (2 log in 60 minutes at 35°C and 90% dilution) was reported, documenting the antifungal action of biclotymol for the first time. Antifungal activity can also have importance in this setting given the risk of opportunistic oral candidiasis in patients receiving an associated antibiotic treatment.

Table I. Minimal inhibitory concentration (MIC) and the amount (absolute and %) of colony forming units (CFU) of survived bacteria at various biclotymol concentrations.

Microorganism	Biclotymol concentration (mg/mL)										MIC, mg/mL	CFU, control
	40.0	20.0	10.0	5.0	2.5	1.25	0.62	0.31	0.15	0.075		
S. pneumoniae	–	–	–	0	0	0	0	0	0	10 (1%)	0.15	900
H. influenzae	–	–	–	0	0	0	0	0	0	7 (2%)	0.15	450
S. pyogenes	–	–	–	0	0	0	0	50 (3%)	125	–	0.62	1500
M. catarrhalis	–	–	–	0	0	0	6 (0.5%)	14	18	125	1.25	1200
S. aureus	0	0	0	0	25 (2%)	163	–	–	–	–	5.0	1700
N. flavescens	0	0	13 (0.5%)	125	275	–	–	–	–	–	20.0	2500
N. perflava	0	0	10 (0.4%)	100	320	–	–	–	–	–	20.0	2500

In addition to its antibacterial effect, biclotymol showed a fast local anti-inflammatory action[8]. Evidence of this effect is supported by the results of a pre-clinical study, which also revealed a remarkable analgesic action at therapeutic doses[9]. Noteworthy, antibacterial and anti-inflammatory/analgesic actions of biclotymol are synergetic for the treatment of sore throat, a condition in which inflammation and pain represent the main symptoms[6,8].

Moreover, since some other phenolic compounds commonly used in pharmaceutical preparations to treat symptoms of sore throat have shown virucidal activity in *in vitro* assessments[3,10,11] biclotymol, as a thymol derivative, might also exert virucidal properties which should be further investigated in a forthcoming study.

Clinical Efficacy

The above-mentioned pharmacological evidence suggests that biclotymol-based preparation presents the antimicrobial properties necessary for the oral symptomatic treatment of bacterial infections of the oropharynx. Clinical activity has been assessed in two well-conducted studies.

Freche and Drweski

Freche and Drewski[6] conducted a first open-label, comparative trial in 40 patients with acute (60%, symptoms < 72 hours) or chronic (40%, symptoms > 15 days) pharyngitis. Patients were assigned to either biclotymol two sprays tid (Hexaspray; n=20) or fusafungine four sprays qid (n=20 patients). Subjective symptoms evaluation and actual anti-inflammatory effect were combined into a single efficacy score ("very good"; "good"; "modest"; "no effect").

At 7-10 days, biclotymol spray was judged as "very good" or "good" in 50% of patients (8% "very good") with acute pharyngitis, *versus* 25% of those on fusafungine (0% "very good"). The advantage for biclotymol spray was observed also in patients with chronic pharyngitis (34.5% "good", *versus* 25% with fusafungine) (Figure 2). Both biclotymol and fusafungine had an excellent local tolerability. The Authors attributed its marked efficacy, at least in part, to its anti-inflammatory effect. Moreover, it can be speculated that the poor efficacy showed by the antibiotic fusafungine can be due to the non-bacterial, viral nature of pharyngitis in most patients. This further emphasizes the importance, in clinical practice, of prescribing agents other than antibiotics and characterized by anti-septic and anti-inflammatory activity like biclotymol.

Chevalier

In a subsequent double-blind, randomized, controlled study[8], 39 patients (mean age, 32 years) with acute pharyngitis were assigned to either biclotymol (two sprays tid) or placebo. Similarly to the previous study, a combined evaluation of treatment efficacy was applied ("very good", "good", "modest", "no efficacy"). Moreover, the analgesic efficacy and the reduction of dysphagia were assessed.

At 4-8 days, 80% of patients treated with biclotymol spray reported a "very good" (35%) or "good" (45%) efficacy. On the other hand, nearly 90% of patients assigned to placebo reported "modest" efficacy (5%) or "no effect" (84%) (Figure 3).

After treatment, 65% of patients on biclotymol were pain-free, as compared with no subjects in the placebo group (Figure 4). A similar advantage was observed for dysphagia (Figure 5). The Authors of this study emphasized that the synergetic anti-bacterial and anti-inflammatory activity of biclotymol largely contributed to the marked efficacy shown by this product. Remarkably, tolerability of biclotymol was judged as excellent.

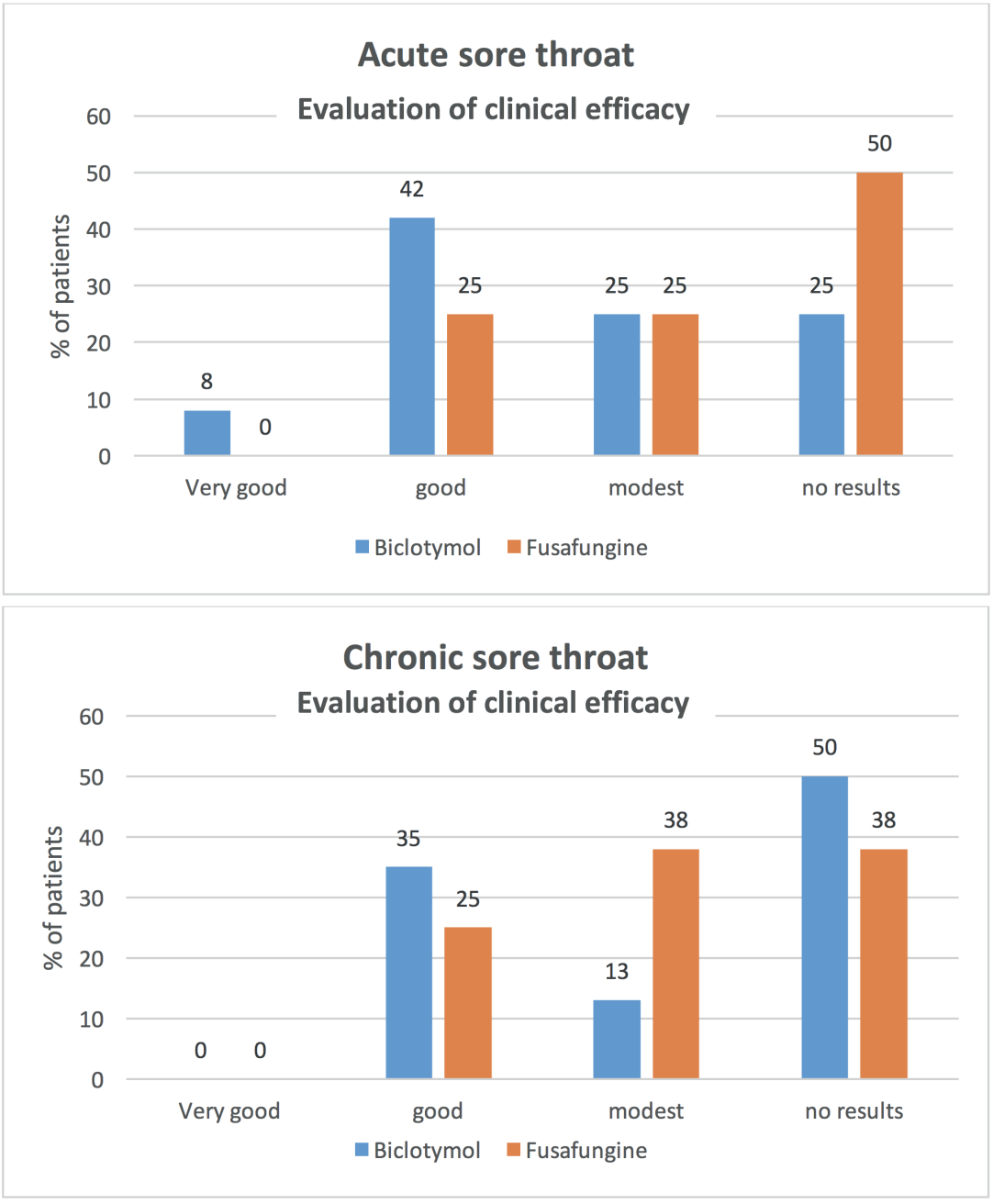

Figure 2. Evaluation of clinical efficacy of biclotymol (n=20) and fusafungine (n=20), in a trial on 40 patients with either acute (Panel A; n=24) or chronic (Panel B; n=16) sore throat[6].

Discussion

Current ESCMID guidelines recommend the prescription of products other than antibiotics in patients with sore throat, reserving antibiotics for patients at risk of complications[1], in order to avoid the adverse effects potentially associated with those latter drugs and limit the onset of resistance[3]. Importantly, in this setting some non-antibiotic treatments can be even more effective than antibiotics themselves[12].

In particular, local treatments with anti-inflammatory and analgesic action may be particularly effective in relieving symptoms[3]. Indeed, since sore throat, of whichever origin, is associated with considerable pain and discomfort. To this end, NSAIDs, paracetamol and antiseptics are recommended for the relief of acute symptoms[1,13].

More specifically, an ideal treatment should provide the symptomatic relief that patients seek as well as treat the cause. Locally-delivered formats such as lozenges and sprays are useful as they enable active ingredients to reach the site of infection directly. The localized delivery allows a lower risk of side effects compared with systemically-acting treatments[3].

Biclotymol is a molecule characterized by a marked antibacterial efficacy, also associated with anti-inflammatory and analgesic actions. Noteworthy, given its mouthwash spray formulation – which allows direct delivery of the active compound to inflamed mucosa – biclotymol provides a fast onset of action and a long-lasting effect, thanks to its peculiar chemical structure which allows its binding to pharyngeal mucosa. Collectively, these properties make biclotymol-based formulations an ideal choice for patients with sore throat.

Two well-conducted studies have assessed biclotymol clinical efficacy in spray formulation. Notably, both studies proved its efficacy. In a study *versus* placebo[8], the analgesic properties of biclotymol were also demonstrated: most patients on this treatment were pain-free after therapy, and the action of biclotymol allowed also a marked reduction of dysphagia. In the other study, *versus* an antibiotic (fusafungine), biclotymol showed better results compared with its competitor in terms of efficacy, in both acute and chronic sore throat[6]. It is interesting to observe that this effect was more evident in patients with acute pharyngitis than in those with chronic conditions: this finding may suggest the early initiation of biclotymol treatment as soon as symptoms become evident. Importantly, tolerability was excellent in both studies, thus ensuring a safe use of this compound also in clinical practice.

Biclotymol mouthwash is currently available in two different spray formulations at the same concentration but with two different flavours (anise and exotic fruits). Its excellent safety profile allows the use of biclotymol even in the paediatric

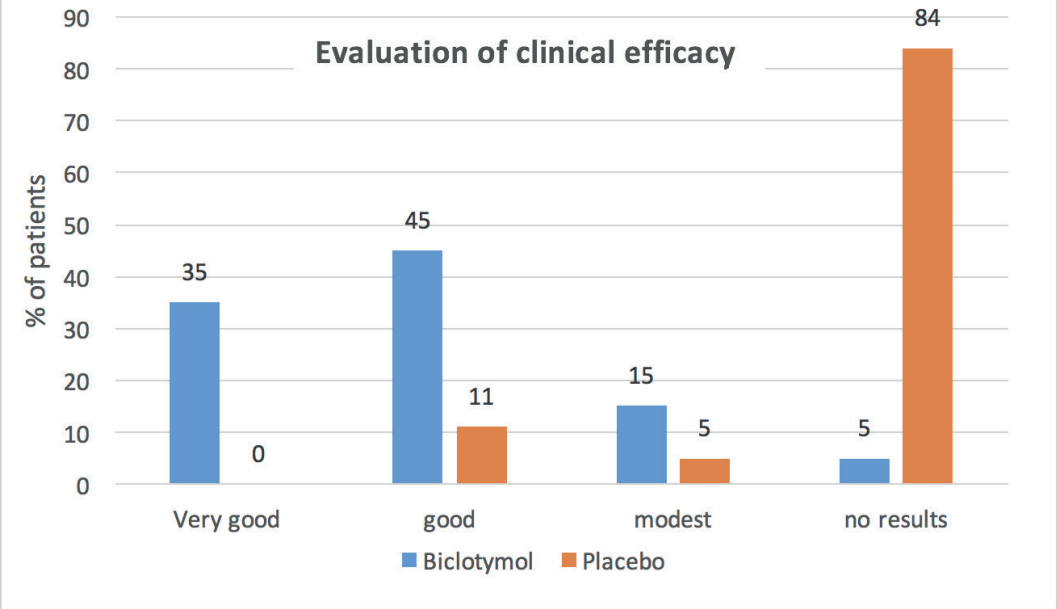

Figure 3. Evaluation of clinical efficacy of biclotymol (n=20) and placebo (n=19) in patients with sore throat[8].

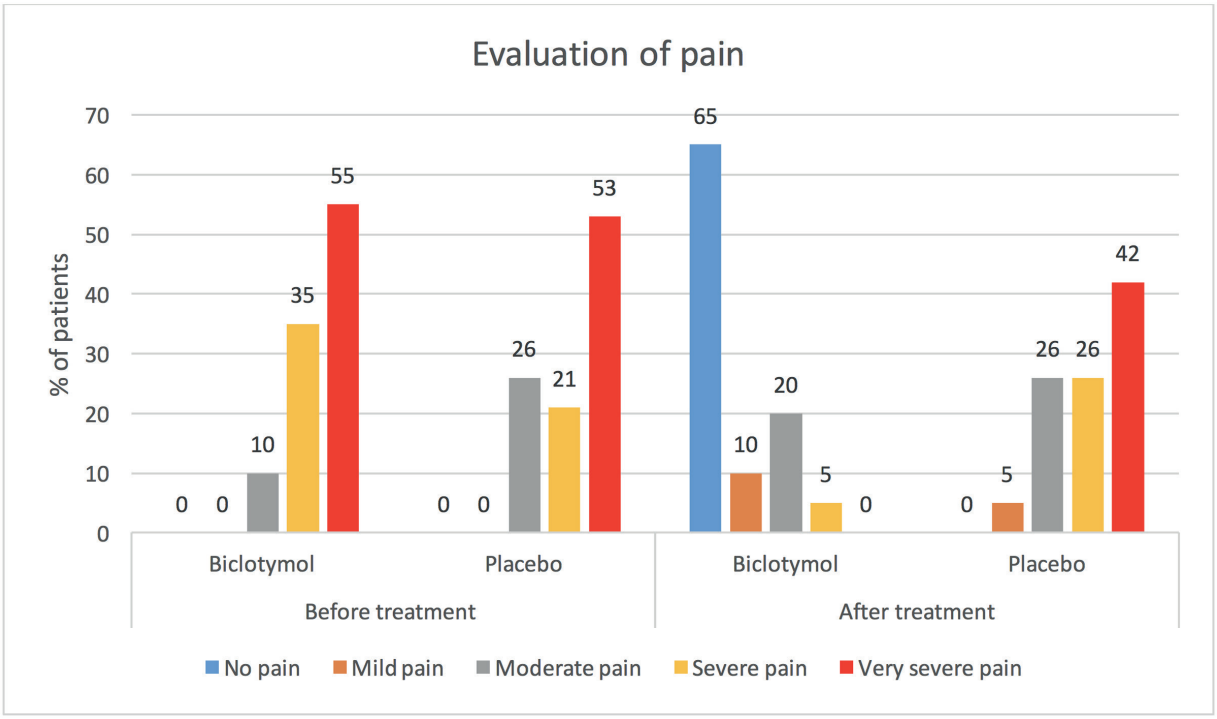

Figure 4. Evaluation of pain intensity in patients with sore throat treated with biclotymol (n=20) or placebo (n=19)[8].

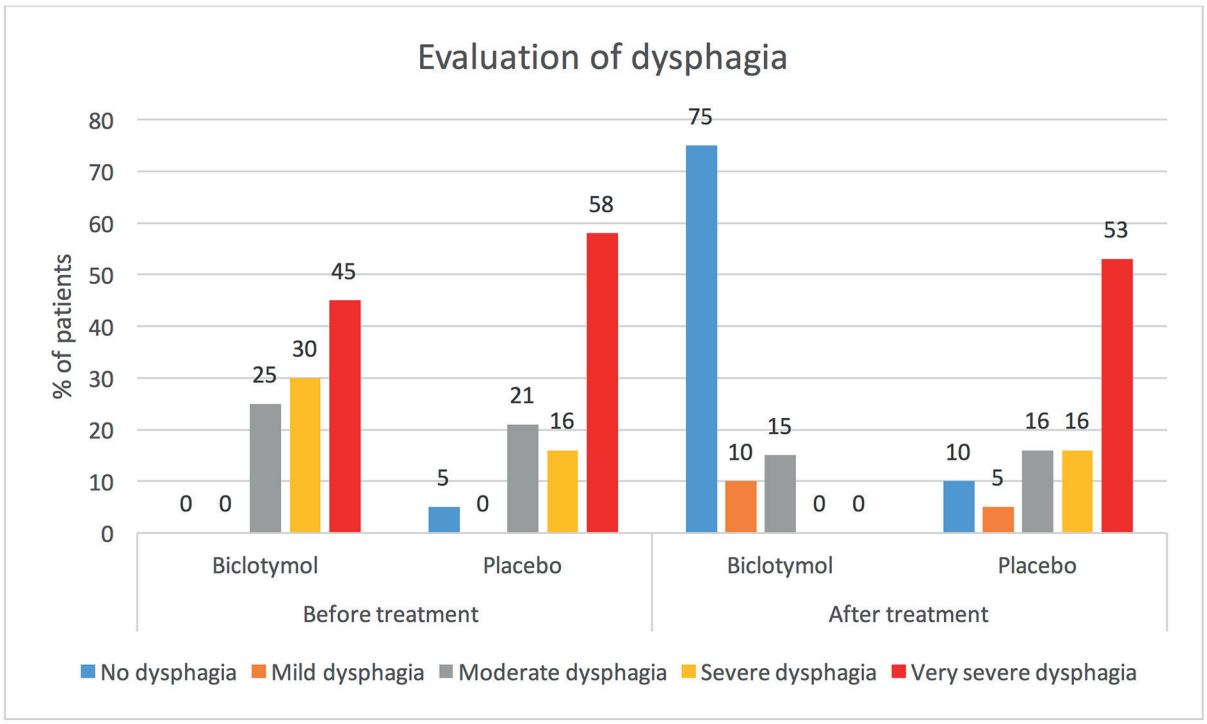

Figure 5. Evaluation of dysphagia intensity in patients with sore throat treated with biclotymol (n=20) or placebo (n=19)[8].

setting, starting from 30 months of age. Of note, biclotymol mouthwash does not contain either corticosteroids or local anesthetics, compounds which could be associated with potential adverse reactions. Similarly to many other medications, as a precaution biclotymol spray should not be taken during pregnancy given the lack of specific studies in this setting.

Treatment for > 5 days is not currently recommended. Therefore, and in line with the more evident efficacy in patients with acute sore throat, early institution of treatment is important to maximize clinical outcomes, thus avoiding symptoms becoming severe. In the everyday practice, patients usually wait for some days before taking a medication for sore throat, and first-line treatment is often a lozenge. On the other hand, mouthwashes and sprays are often perceived as 'second-line' therapies for sore throat if lozenge have shown poor efficacy. However, given the fast onset of action and the long-lasting, multiple effects of biclotymol, this treatment may be considered as a front-line therapy, either alone or in combination with a lozenge remedy. In fact, biclotymol can be sprayed directly on the irritated mucosa, thus ensuring a prompt relief from discomfort, while lozenge supplements this action in the whole area.

Another biclotymol-based formulation is currently available, namely a lozenge containing biclotymol, lysozyme chlorohydrate and enoxolone (Hexalyse, Laboratoires Bouchara Recordati, France). Lysozyme has a well-established anti-bacterial and anti-viral action[14,15]. Moreover, lysozyme can exert and efficient immune-modulatory activity[16]. Enoxolone, also known as glycyrrhetinic acid, is a pentacyclic triterpenoid derivative obtained from the hydrolysis of glycyrrhizic acid (from the herb liquorice), also characterized by antibacterial, antiviral and anti-inflammatory action[17,18]. The multiple activity of biclotymol may synergize well with the above-discussed actions of lysozyme and enoxolone, thus granting a wide and multi-targeted anti-bacterial and anti-viral action.

Given the antiseptic, anti-inflammatory and analgesic properties of biclotymol, the use of preparations based on this molecule in other settings (e.g., after local surgery such as tonsillectomy) has been successfully tested in clinical practice, although these preliminary experiences have not been fully documented yet. Targeted studies on other indications appear eagerly awaited, in line with ongoing research in this field[19].

Conclusions

According to the current ESCMID guidelines, the prescription of products other than antibiotics is recommended, especially in patients with less severe presentation of sore throat[1,20].

While other trials can be conducted to further investigate the pharmacological profile and the efficacy of biclotymol treatment, we believe that enough evidence exists to recommend the use of biclotymol-based formulations as a prompt, effective and safe first-line option for the treatment of sore throat. Noteworthy, thanks to its excellent safety profile and fast onset of action, biclotymol also represents a suitable choice for the treatment of sore throat in paediatric patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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