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The development of new clinical instruments in laryngopharyngeal reflux disease: The international project of young otolaryngologists of the International Federation of Oto-rhino-laryngological Societies

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ABSTRACT

Introduction: To analyze the epidemiological characteristics of placebo controlled randomized trials (RCTs) that evaluated the effectiveness of medical treatments over placebo in laryngopharyngeal reflux (LPR).

Material and methods: PubMed, Cochrane database, and Scopus were assessed for subject headings using the PRISMA recommendations. Placebo RCTs published between 1990 and 2018 describing clinical evolution throughout LPR treatment were extracted and analyzed for evidence-based level, number of patients, inclusion and exclusion criteria, gender, age, symptoms and signs used as therapeutic outcomes, and treatment schemes.

Results: The database search identified 15 placebo RCTs with a total of 763 patients. The mean age of patients was 48.59 years and 52.68% of patients were female. Among the 15 placebo RCTs, 9 have demonstrated a partial or total superiority of a medical treatment over placebo. Most of authors based the LPR diagnosis on symptoms and signs without additional examination. Our analysis reveals an important heterogeneity between studies with regard to the diagnosis criteria, treatment schemes and signs and symptoms used as therapeutic outcomes. Many commonly reported signs and symptoms related to LPR were not used as therapeutic outcomes. Half of the authors did not prescribe diet and behavioral changes along the treatment.

Conclusion: The controversy in the RCTs about the superiority of medical treatment over placebo in LPR disease is probably due to discrepancies in the diagnosis method, exclusion criteria, therapeutic schemes and the lack of comprehensive tools for the assessment of signs and symptoms. In this context, the LPR Study Group of Young-Otolaryngologists of the International Federations of Oto-Rhino-Laryngological Societies developed two new instruments to precisely assess signs and symptoms throughout the treatment. These two instruments could be used in future trials comparing medical treatment over placebo in LPR disease.

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1. Introduction

Laryngopharyngeal reflux (LPR, also called silent reflux, reflux laryngitis) is an inflammatory disease characterized by the back flow of gastric and/or duodenal content into the laryngopharynx where it comes in contact with mucosa of the upper aerodigestive tract. This disease affects 10% of patients being treated in otolaryngology, and more than 50% of patients suffering from voice disorders in the United States [1,2]. Today, the prevalence of LPR disease in Europe remains unknown. On the clinical plane, the acidic, bile or mixed acid/non-acid gaseous refluxes cause acute and/or chronic irritation to the mucosa of the upper digestive tract, manifesting as different complaints or clinical symptoms [3]. The main symptoms of LPR are globus, dysphonia, dry throat, cough, and throat clearing as well as an excess of viscous secretions in the throat [1,4,5]. Heartburn and acid reflux are not systematic, as they only affect 50 to 86% of patients [6–8]. Their absence does not rule out diagnosis. On a semiological plane, LPR is characterised by different endoscopic signs such as hypertrophy and erythema of the posterior commissure, ventricular bands, arytenoids, epiglottis, as well as the presence of thick and sticky mucus at the level of the endolarynx or the piriform sinuses [1,4,5].

The diagnostic and therapeutic approaches of LPR are currently the object of a double controversy. On one hand, impedance pH monitoring remains controversial because of non-negligible rates of false positives and false negatives, the absence of a clinical threshold considered as pathological, and the absence of correlation between the impedance pH monitoring results, and the signs and symptoms of LPR patients [8–11]. On the other hand, the efficiency of proton-pump inhibitors on LPR has not yet been demonstrated because of uncertain results in different randomized placebo-controlled studies, which have taken place over the last two decades [12,13]. The controversial results of placebo-controlled studies could be explained by three hypotheses. Firstly, the absence of a complete clinical tool allowing for the evaluation of all signs and symptoms during the course of treatment. Secondly, the administration of diet and lifestyle changes in the placebo group could alter the interpretation of results, given the demonstrated therapeutic impact of the plan. [5,14,15]. Finally, major interstudy differences in the inclusion and exclusion criteria of patients could also guide the selection of subgroups of patients, distinguishing some from others by their different therapeutic responses to proton-pump inhibitors (PPIs).

Considering these three hypotheses, the aim of this study is to analyze the epidemiological, clinical and therapeutic characteristics of placebo-controlled randomized trials (RCTs) carried out in the context of LPR. Following an analysis of literature, we suggest improvement tips for the treatment of LPR, with the help of new clinical tools.

2. Material and methods

2.1. Research strategy

A literature review has been carried out to identify each scientific article published between 1990 and 2018 in English, or French on PubMED, Scopus, and the Cochrane Library. The key words used were 'laryngopharyngeal', 'reflux', 'laryngitis', 'gastroesophageal', 'placebo' and 'treatment'. For each study, we identified the team carrying out the study, the name, average age and gender of the patients to avoid multiple inclusions. Supplementary Fig. 1 shows the charflow of the study carried out using PRISMA Statement [16].

2.2. Selection, extraction and analysis of data

In review, we focused on placebo RCTs studying the impact of a medical treatment on patients with suspected or confirmed LPR disease.

In terms of the existing controversy surrounding the diagnosis of LPR, we wished to remain as inclusive as possible in terms of the diagnostic methods used in placebo RCTs. The diagnosis could be based either on impedance pH monitoring (LPR patients) or on laryngoscopic signs and symptoms of LPR (patients suspected to have LPR). Moreover, each author must have carefully excluded patients who are already being treated for LPR, having undergone antireflux surgery or those suffering or being treated for cancer of the upper aerodigestive tract. We have not included studies that exclusively concern voice professionals or children. Two authors have evaluated the summaries of different publications identified by key words (JRL & MRB). Only those studies that met our inclusion and exclusion criteria have been analyzed with the full text of the publication.

For each of these studies, the characteristics of the patients (number, age, gender), of the study (type of study and level of evidence), the LPR diagnostic method, the inclusion and exclusion criteria, the treatment (type and duration) and the clinical scales have been identified. The level of EBM evidence of each study (going from Ia to V) has been determined using recommendations from the Oxford Evidence-Based Medicine Center [17].

2.3. Therapeutic interventions

LPR patients had to be treated either by placebo or by medication, which could include the exclusive or simultaneous use of PPIs, antihistamines, alginates or other nonsurgical treatment. We have identified the use of diet and behavioral changes.

2.4. Identification of clinical evaluations, inclusion and exclusion criteria

To be included, the studies must evaluate the impact of the treatment using clinical evaluations (symptoms and/or signs) supported or not by standardized instruments. Inclusion and exclusion criteria for the studies have been analyzed to study the profiles of the included patients. More precisely, we have analyzed whether the authors have excluded some conditions that could lead to complaints similar to those of LPR, such as the presence of an infectious pathology of the upper respiratory tract during the month preceding the consultation (group 1), frequent consumption of alcohol or tobacco, or the presence of an active allergy (group 2), use of antireflux medication at the time of inclusion in the study (group 3), history of pharyngolaryngeal trauma, cancer of the upper respiratory tract or otolaryngological surgery (group 4), the presence of benign vocal fold lesions (group 5) and the presence of a neurological or psychiatric pathology (group 6).

3. Results

3.1. Results of the research

Systematic research on our databases identified 72 studies carried out on LPR. Among these we have selected 15 placebo-controlled studies. The included placebo-RCTs are Ib evidence level, according to the recommendations of the Oxford Evidence-Based Medicine Center [17]. With the exception of two studies [18,19], all publications are available on PubMED. The epidemiological characteristics of these 15 placebo RCTs [18–32] are described in Table 1. Eight studies were carried out in North America (7 in the United States and 1 in Canada), 3 in Asia (China, Taiwan, and India), 2 in

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