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The role of an oral formulation of hyaluonic acid and chondroitin sulphate in the treatment of patients with laryngopharyngeal reflux

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ABSTRACT:

Introduction: Proton pump inhibitors (PPIs) have become an important breakthrough in the treatment of gastroesophageal reflux disease (GERD). However, in patients with laryngopharyngeal reflux (LPR) – one of the extraesophageal variants of the disease – the efficacy of PPI is incomplete or limited and alleviation of symptoms requires additional medications. As of today, the importance of hyaluronic acid (HA) and chondroitin sulphate (CS) and their role in mucosal damage healing, most particularly within the larynx, is being highlighted.

Objective: The objective of the study was to assess the outcomes of treatment in LPR patients receiving a combination of hyaluronic acid and chondroitin sulfate (HA + CS) on a bioadhesive carrier.

Material and methods: A total of 51 patients (18 males and 33 females) aged 25–75 years and presenting with LPR symptoms further confirmed in a laryngovideoscopic examination, were included in the study. Patients were qualified for the study on the basis of reflux symptom index (RSI) of above 13 and reflux finding score (RFS) of above 7. Patients were recommended to use the HA + CS combination product for 14 days and were evaluated after this time.

Results: Symptoms suggestive of significant or severe problem (RSI of 4 or 5) before the treatment included: throat clearing (48 patients; 90.19%), hoarseness (29 patients; 56.86%) and cough after eating/cough while lying down (37 patients; 72.50%). After the treatment, patients reported a moderate impact of the above symptoms on their everyday functioning ($P < 0.001$). Symptoms such as pharyngeal mucus presence, acute cough, sensation of foreign body in the throat, while declared as moderate at baseline (score of 3) resolved to mild (score of 1) following the supportive treatment ($P < 0.001$). Total RSI after the treatment was assessed as borderline for LPR diagnosis (median 13, range 12–15). Although patients were not completely freed of their reflux symptoms, a significant reduction in symptoms was achieved in the entire study group. Prior to the treatment, the most common morphological changes within the larynx included redness/congestion, vocal fold edema and posterior commissure hypertrophy. These changes were observed in all patients. After the treatment, the RFS fell below the LPR diagnostic threshold (median 6, range 5–7). Compared to baseline values (median 9, range 8–10), significant improvement of laryngeal changes was observed in nearly the entire study group ($N = 50$; 98.04%) ($P < 0.001$).

Conclusions: The combination product consisting of hyaluronic acid and chondroitin sulfate on a bioadhesive acts locally to significantly reduce laryngopharyngeal reflux symptoms, particularly in patients with chronic cough, throat clearing, and hoarseness. In addition, by lining the laryngeal mucosa with a protective layer, the product facilitates better hydration as well as faster healing and regeneration of the mucosal membrane, thus leading to a reduction or resolution of morphological changes within the larynx.

KEYWORDS: chondroitin sulphate, endoscopy of the larynx, gastroesophageal reflux, hyaluronic acid, laryngopharyngeal reflux, treatment

ABBREVIATIONS

COPD – chronic obstructive pulmonary disease
CS – chondroitin sulphate
GERD – gastroesophageal reflux disease
HA – hyaluronic acid
LPR – laryngopharyngeal reflux
MII – multichannel intraluminal impedance
NERD – nonerosive reflux disease
PPI – proton pump inhibitors
RFS – reflux finding score
RSI – reflux symptom index

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INTRODUCTION

For many years, gastroesophageal reflux disease (GERD) has been one of the most common disorders of the upper gastrointestinal tract. In some regions of the world, owing to the increasing frequency and prevalence, GERD has grown nearly to the size of an epidemic and is thus referred to as "the disease of the new millennium". The disorder affects about 20% of the population in Western Europe and North America as compared to 10% in South America and only 2.3 to 6.2% in Asia [1]. In highly developed countries, symptoms occur every day in about 7 to 10% of the population, once a week in about 20%, and once a month in about 40% of the population [2]. The average prevalence of reflux in children is 8%. In Poland, 34% of patients reporting at family medicine facilities present with symptoms warranting the diagnosis and treatment of GERD. The incidence of GERD is estimated to have tripled compared to the 1990s [3].

GERD consists in the stomach contents being regurgitated upwards into the esophagus to cause troublesome symptoms and/or complications which negative affect patient's well-being and occur more frequently than once a week. According to the Montreal classification, reflux disease can be classified as either esophageal (typical) or extraesophageal (atypical) [1, 4]. The former include symptomatic syndromes (typical reflux syndrome, epigastric pain and sleep disturbance caused by the reflux) and syndromes resulting from esophageal damage (esophageal inflammation, esophageal stenosis, Barrett's esophagus, adenocarcinoma). Extraesophageal syndromes include those for which the causal relationship with reflux was demonstrated (reflux cough syndrome, laryngeal syndrome, asthmatic syndrome, dental erosion syndrome) and those for which such a relationship has not been sufficiently proven (pharyngitis, paranasal sinusitis, pulmonary fibrosis, recurrent otitis media). Clinical signs of the disease may vary in severity from occasional episodes to persistent problems.

Laryngopharyngeal reflux (LPR), also known as atypical reflux, gastropharyngeal reflux, laryngeal reflux, or pharyngolaryngeal reflux, is one of the extraesophageal forms of the disorder. LPR is considered a special case of GERD as both disorders are characterized by different risk factors, pathophysiology, symptoms, and treatment [5]. LPR is defined as gastric contents being regurgitated upward into the upper respiratory tract (larynx, throat, nasopharynx, sinuses, middle ear) with secondary damage to the mucosa which, upon dysfunction of protective mechanisms, is more sensitive to hydrochloric acid and pepsin than esophageal mucosa. Direct exposure of the larynx and the airways to the stomach contents leads to secondary irritation and damage to the laryngopharyngeal mucosa. In contrast to the mucous membranes of the esophagus, this damage is irreversible. Given the anatomical and functional differences between respiratory and gastrointestinal epithelium, even a minor laryngopharyngeal reflux can cause laryngeal mucositis which then persists for up to several weeks. Pathological reflux leads to the development of clinical symptoms and morphological changes. Aspiration of irritant gastric contents may occur particularly at night, when esophageal sphincters are relaxed. Larynx was shown to be much more sensitive to acids compared to the esophagus and as few as three episodes are sufficient to cause severe inflammation and damage to the organ's epithelium [6]. The risk factors of the disease include the frequent use of voice, smoking, frequent respiratory infections, allergies, pet animals, chronic exposure to air conditioning, secretions being drained down the posterior wall of the throat (symptoms of chronic paranasal sinusitis), new environmental conditions, and positive history of GERD [7, 8].

LPR symptomatology is much more varied compared to that of GERD and includes a number of unusual symptoms such as morning voice disorders, cough after meals and in the morning, throat dryness, sensation of a foreign body/obstruction within the throat, constant urge to clear one's throat, secretion flowing down the posterior wall of the throat, sore throat, unpleasant smell from one's mouth, choking, dyspnea with nocturnal exacerbations. These frequently lead to glottic stenosis, upper and lower airway inflammations (pharyngitis, laryngitis, sinusitis, bronchitis, idiopathic pulmonary fibrosis, COPD, aspirating pneumonia), otitis with effusion, dental and periodontal diseases, or sleep apnea syndrome [9]. The most common symptoms in the course of LPR include drainage of secretion down the back of the throat, cough, hoarseness, and sensation of foreign body within the throat. Hoarseness is variable in intensity as it is significantly increased immediately after awakening in the morning hours and markedly improves during the day.

Laryngological diagnosis of LPR is based on a detailed interview and laryngological examination optionally supplemented by gastrological diagnostics. The role of videolaryngoendoscopic examination is emphasized as esophagogastroscopy results are often unremarkable in patients with laryngopharyngeal reflux. The intensity of potential inflammatory lesions within the esophagus is not correlated with the severity of pathological lesions within the larynx. In the natural history of LPR, laryngoscopic evaluation reveals swelling and erythema of arytenoid cartilage and interarytenoid fold, edema of the posterior commissure, erythema and edema of the vocal cords, infraglottic edema (*pseudosulcus*), vocal process granulomas, contact ulcers, dense mucus accumulation, and shallow ventricles of Morgagni.

To date, it has not been possible to create a gold standard for the diagnosis of reflux disease and thus a variety of diagnostic methods are used. In addition to clinical evaluation of the disease symptoms and videoendoscopy, these include attempts at proton pump inhibitor (PPI) pharmacotherapy, 24-hour esophageal pH test and multichannel impedance measurements (multichannel intraluminal impedance; MII) [10]. Esophageal manometry is performed prior to each endoesophageal examination.

Patients with reflux disease should be managed by a multispecialist team consisting of a gastrologist, a laryngologist, a phoniatrician, and, in some cases, a psychologist. The treatment of reflux disease is based on non-pharmacological management largely consisting in lifestyle changes, particularly diet modifications. It is aimed at eliminating conditions that promote reflux and includes an antireflux diet (regular, smaller-volume meals taken 4–5 times a day, avoidance of spicy and sweet foods and soft drinks, last meal being consumed not later than 2–3 hours before sleep), avoidance of physical exercise immediately after meals, and body weight reduction in overweight and obese people [11].

Depending on the severity of LPR symptoms, pharmacotherapeutic directions include suppression of gastric acid secretion, prokinetic effects, mucosal protection, and visceral pain reduction. Proton pump inhibitors (PPIs) are the primary group of pharmaceuticals used in the treatment of GERD due to their superior efficacy in the suppression of gastric hydrochloric acid. In most patients, PPIs facilitate prompt resolution of clinical symptoms regardless of the level of esophageal inflammation, an improvement in the quality of life and the healing of the mucous membrane within the esophagus. Prompt clinical improvement confirms the validity of the diagnosis and reduces the number of diagnostic tests [3]. The importance of supportive treatment, including H_2 blockers, over-the-counter alkalizing agents (alginates, sucralfate, aluminum compounds, magnesium compounds, calcium compounds) and preparations containing hyaluronic acid with chondroitin sulphate, has been highlighted in the management of reflux disease [12, 13, 39]. Indications for laparoscopic fundoplication should be considered upon the absence of response to pharmacological treatment, frequent recurrence of reflux symptoms, concomitant hiatal hernia, and confirmation of clinically relevant non-acid reflux.

OBJECTIVE

The objective of the study was to assess the intensity/severity of signs and symptoms (morphological changes within the larynx) in patients before and after 2 weeks of hyaluronic acid and chondroitin sulfate (HA + CS) combination treatment in patients with laryngopharyngeal reflux.

MATERIAL AND METHODS

A total of 51 patients (18 males and 33 females) aged 25–75 years (mean age 45.4 ± 14.98) and presenting with LPR symptoms further confirmed in a laryngovideoscopic examination, were included in the study. The inclusion criteria were: age of above 18, no malignancies or inflammations within the upper respiratory tract and upper gastrointestinal tract, absence of inhaled or food allergies, history of symptoms suggestive of LPR experienced for at least 3 months and at least 3 times a week, and presence of morphological lesions within the larynx. Twenty-four (47.05%) patients were receiving proton pump inhibitors at the time of their inclusion in the study. In these patients, treatment was supplemented with a combination of hyaluronic acid and chondroitin sulphate (HA + CS) in a bioadhesive suspension of poloxamer 407 which facilitates the adhesion of the product to the mucous membrane within the upper GI tract. The remaining patients had not been treated for reflux in the pre-study period or had discontinued PPIs due to their ineffectiveness more than 3 months before the study. Only the above-mentioned combination product was included in the treatment of all patients in this study.

As part of study qualification procedures, each patient was surveyed and assessed using the reflux symptom index (RSI) as developed by Belavsky et al. [14]. Patients qualified for the study had total RSI scores of more than 13. As part of the assessment of each symptom, patients were asked to assess the degree of being affected by the particular problem within the last month using the following scale: no symptoms (0 points), slight symptoms (1 points), mild symptoms (2 points), moderate symptoms (3 points), serious symptoms (4 points), and severe symptoms (5 points).

Reflux finding score (RFS) was used to assess the severity of laryngeal lesions [6]. Videolaryngoscopy-based score of above 7 was considered positive for the diagnosis of LPR.

The study group consisted of patients with morphological changes being observed in videofiberoscopic examination of the larynx and pharynx, including redness/congestion, edema of vocal folds, infraglottic edema, posterior commissure hypertrophy, diffuse laryngeal edema, granulomas, vestibular obliteration, and thick intralaryngeal mucus.

Patients were recommended to use the medicinal product three times during the day up to one hour after a meal (breakfast, lunch, and dinner) as well as immediately before going to bed for the night.

The study was approved by the Bioethics Committee (decision no. RNN/396/19/KE).

The results were subjected to statistical analysis. Ordinal variables were presented as medians and interquartile intervals (25–75%) and analyzed using Wilcoxon signed-rank test. The test compared the changes in individual scale components and total scores before and after the treatment. All statistical analyses were carried out using Statistica 13.1 (StatSoft) software package. Statistical significance was defined as $P < 0.05$.

RESULTS

Changes in the symptoms of laryngopharyngeal reflux before and after 2 weeks of treatment with combination of hyaluronic acid and chondroitin sulphate are summarized in Tab. I. Tab. II presents the same changes according to patient gender. The most commonly reported symptom in the study group was throat clearing reported as either serious (43 subjects; 84.31%) or severe (5 patients; 5.88%) by a total of 48 patients (90.19%). The second most predominant symptom was hoarseness reported as serious by 26 (50.98%) patients and moderate by 17 (33.33%) patients. As few as 5 people (9.80%) rated this condition as mild, in contrast to another 3 subjects (5.88%) who considered it severe. However, the greatest therapeutic benefit from the combination treatment was observed in the latter group as patients reported hoarse throat being reduced to a moderate and thus acceptable level. Thus, the symptoms suggestive of significant or severe problem (RSI of 4 or 5) before the treatment included: throat clearing (48 patients; 90.19%), hoarseness (29 patients; 56.86%), and cough after eating /cough while lying down (37 patients; 72.50%). After the treatment, patients reported a moderate impact of the above symptoms on their everyday functioning. Baseline symptoms such as the presence of mucus within the throat, persistent cough, or the sensation of foreign body within the throat were referred to as moderate

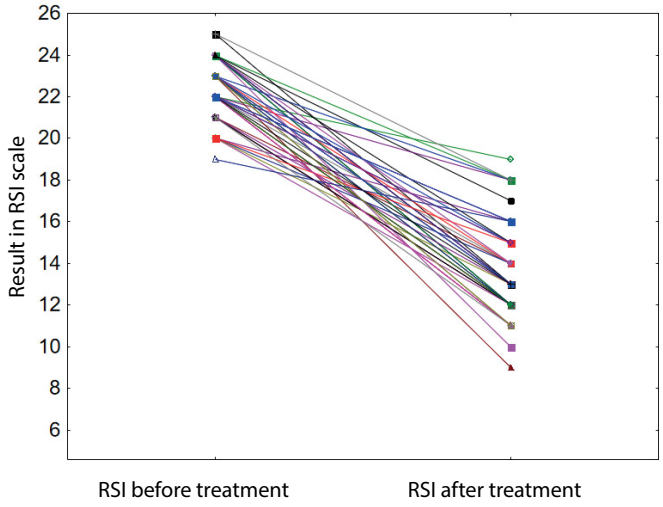

Fig. 1. Changes in the overall RSI scores and trend lines in individual patients with LPR (N = 51) before and after treatment with hyaluronic acid and chondroitin sulphate.

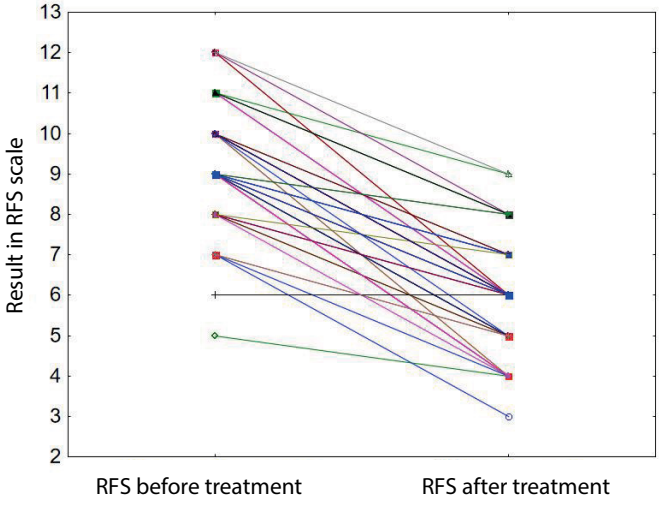

Fig. 2. Changes in the overall RFS scores and trend lines in individual patients with LPR (N = 51) before and after treatment with hyaluronic acid and chondroitin sulphate.

(3 points). After the supportive treatment administered to promote the healing of the mucous membrane, the perceived level of these symptoms decreased significantly to very mild (1 point) ($P < 0.001$).

The study group patients reported a low level of swallowing disorders referred to as throat dryness and tickling (1 point; 25 patients; 49.01%) during the last month. The least frequently reported symptoms included heartburn (14 patients; 27.45%) and dyspnea (2 patients; 3.92%). Incidents of heartburn, very mild in all cases (1 point), were reported in 14 patients (27.45%). The improvement, interpreted by patients as resolution of this symptom experienced over the 2 weeks of treatment, was reported by 3 individuals. The others reported isolated incidents with very low intensities.

After the treatment, the threshold RSI limit required for the diagnosis of LPR (median 13, range 12–15) was established, with reflux disease being diagnosed above these values. Therefore, although patients were not completely freed of their reflux symptoms, a significant reduction in symptoms was achieved in the entire study group (N = 51). No differences were found between the individual symptoms of laryngeal reflux according to patients' gender (Tab. II.). Changes in the overall score and the RSI trend lines in individual patients with LPR (N = 51) before and after treatment with hyaluronic acid and chondroitin sulphate are provided in Fig. 1. They are indicative of reduction – albeit not always statistically significant – in the symptoms for each component of the RSI scale (Tab. I.).

The greatest benefit from the HA+CS combination administered on a bioadhesive substrate was observed in patients in whom the combination was administered in addition to previous PPI therapy. They reported a significant reduction in symptoms, particularly in relation to pharyngeal dryness and obstruction, throat clearing, and cough.

Morphological laryngeal changes in LPR patients before and after 2 weeks of combined treatment are presented in Tab. III. Tab. IV. presents the same changes according to patient gender. Changes observed most frequently in laryngeal videoendoscopy included redness/congestion of the posterior laryngeal segment, swelling of vocal folds and hyperplasia of the posterior commissure; all these changes were observed in all 51 patients (100%). Diffuse redness of vocal folds (4 points) was observed at baseline in 40 patients (78.43%) as compared to 11 (21.57%) patients in whom the changes were restricted to arytenoid cartilages (2 points). Following the treatment, the initially diffuse changes were restricted to arytenoid cartilage in 35 patients (68.63%) while remaining unchanged in another 10 patients (19.60%). In 5 patients (9.80%), complete resolution of baseline changes in the form of vocal fold reddening restricted to arytenoid cartilage was observed.

The second most dominant type of baseline changes consisted in swelling of vocal folds referred to as serious (3 points) in 32 (62.75%) patients and moderate (2 points) in 19 (37.25%) patients. Following 2 weeks of treatment with the HA + CS combination, serious changes persisted in 7 patients (13.72%), while being reduced to moderate or mild in the remaining 25 patients. Although as much as one half of baseline-moderate changes were reduced to mild intensity, they could not be resolved altogether. No complete resolution of vocal fold swelling was observed in either of the patients.

Posterior commissure hypertrophy was observed in all patients; however, these changes were neither severe nor obstructive; instead, they were either moderate in 38 (74.51%) patients, or mild in 13 patients (25.49%). Following the treatment, 18 patients (35.29%) experienced a reduction in the intensity of hypertrophy from moderate (2 points) to mild while the remaining 20 patients (39.21%) experienced no change in the severity of lesions. Granulomas were another group of lesions observed in the study group as they occurred 5 patients (9.80%) at baseline and resolved in 2 of these patients following the treatment. However, it must be highlighted that said lesions were relatively small, up to 3 mm in diameter (Fig. 3.).

Other changes such as thick mucus present within the larynx or mild diffuse laryngeal edema (1 point) were observed in 7 (13.73%)

Tab. I. Comparison of results obtained in individual domains of RSI scale and total score in patients with laryngopharyngeal reflux (N = 51).

VARIABLES	BEFORE TREATMENT [MEDIAN (25-75%)]	AFTER TREATMENT [MEDIAN (25–75%)]	IMPROVEMENT (N)	P
hoarseness	4 (3–4)	2 (1–2)	39	<0,001
grunting	4 (4–4)	2 (2–3)	40	<0,001
mucus in the throat	3 (3–4)	2 (2–3)	29	<0,001
dysphagia	1 (1–2)	1 (0–2)	17	<0,001
cough after eating/lying down	4 (3–4)	2 (2–3)	37	<0,001
dyspnea	0 (0–0)	0 (0–0)	1	0,317
nagging cough	3 (3–4)	1 (1–2)	42	<0,001
feeling of obstruction in the throat	3 (2–3)	1 (1–2)	42	<0,001
heartburn, acid in the throat	0 (0–1)	0 (0–0)	3	0,109
Total RSI	22 (22–24)	13 (12–15)	51	<0,001

Tab. II. Comparison of results obtained in individual domains of RSI scale and total score depending on the sex of patients with laryngopharyngeal reflux (N = 51).

	MEN				WOMEN			
VARIABLES	BEFORE TREATMENT [MEDIAN (25–75%)]	AFTER TREATMENT [MEDIAN (25–75%)]	IMPROVEMENT (N)	P	IMPROVEMENT (N)	BEFORE TREATMENT [MEDIAN (25–75%)]	AFTER TREATMENT [MEDIAN (25–75%)]	P
hoarseness	4 (3–4)	2 (2–2)	16	<0,001	23	4 (3–4)	2 (1–2)	<0,001
grunting	4 (4–4)	3 (2–3)	13	0,001	27	4 (4–4)	2 (2–2)	<0,001
mucus in the throat	3 (3–4)	2 (2–3)	13	0,001	16	3 (3–4)	3 (2–3)	<0,001
dysphagia	1 (1–1)	1 (0–1)	6	0,028	11	2 (1–2)	1 (0–2)	0,003
cough after eating/lying down	4 (3–4)	2 (2–2)	15	0,001	22	4 (4–4)	2 (2–3)	<0,001
dyspnea	0 (0–0)	0 (0–0)	0	1	1	0 (0–0)	0 (0–0)	0,317
nagging cough	3 (3–4)	1 (1–2)	17	<0,001	25	3 (3–4)	1 (1–2)	<0,001
feeling of obstruction in the throat	3 (2–3)	1 (1–2)	15	0,001	27	3 (2–3)	1 (1–2)	<0,001
heartburn, acid in the throat	0 (0–1)	0 (0–1)	1	0,317	2	0 (0–0)	0 (0–0)	0,18
Total RSI	22 (21–23)	13 (12–14)	18	<0,001	33	23 (22–24)	13 (12–15)	<0,001

and 13 patients (25.49%), respectively. No reduction in these symptoms was observed as the lesions remained stable despite the treatment. No advanced lesions such as infraglottic edema or vestibular obliteration were observed in the study group.

After the HA + CS treatment, the RFS fell below the LPR diagnostic threshold (median 6, range 5–7). Compared to baseline values (median 9, range 8–10), significant improvement of laryngeal changes was observed in nearly the entire study group (N = 50; 98.04%) (P < 0.001).

No differences were observed in the presentation of morphological lesions in the natural history of laryngopharyngeal reflux between male and female patients (Tab. IV.). Changes in the overall score and the RFS trend lines in individual patients with LPR (N = 51) before and after treatment with HA + CS combination are provided in Fig. 4. They are indicative of reduction — albeit not always statistically significant — in morphological lesions constituting each of the components of the RFS scale (Tab. III.).

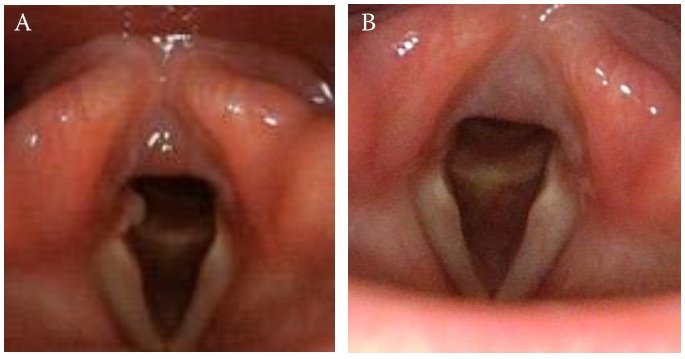

Fig. 3. Fiberolaryngoscopic image revealing lesions within the posterior commissure region manifested as mucosal congestion and right vocal process granuloma: (A) at baseline, and (B) following the treatment with hyaluronic acid and chondroitin sulphate combination administered in monotherapy 4 times a day over 14 days. Regression of granuloma and resolution of mucosal congestion within the posterior segment of the larynx can be observed (B).

DISCUSSION

In patients with laryngopharyngeal reflux, regurgitation of gastric contents into the larynx is responsible for morphological lesions such as dilatation of blood vessels within the mucosal and submucosal membranes, ecchymoses, perivascular parenchymal edema, inflammatory transudate, and fibroblast infiltration leading to fibrosis, thickening, and deformation of laryngeal structures followed by squamous metaplasia of ciliary epithelium along with the hypertrophy and secondary atrophy of muciparous glands. These lesions are manifested as dry throat with burning or tickling sensation, clearing one's throat, cough, and altered voice

Tab. III. Comparison of results obtained in individual domains of RFS scale and total score in patients with laryngopharyngeal reflux (N = 51).

VARIABLES	BEFORE TREATMENT [MEDIAN (25–75%)]	AFTER TREATMENT [MEDIAN (25–75%)]	IMPROVEMENT (N)	P
subglottic edema 0 – absent, 2 – present	0 (0–0)	0 (0–0)	0	1
atrial obliteration 0 – none, 2 – partial, 4 – total	0 (0–0)	0 (0–0)	0	1
redness/hyperemia 0 – none, 2 – only arytenoid cartilage, 4 – diffuse	4 (4–4)	2 (2–2)	35	<0,001
swelling of the vocal folds 0 – none, 1 – mild, 2 – moderate to severe, 3 – significantly severe, 4 – polypoid	3 (2–3)	1 (1–2)	33	<0,001
Diffuse laryngeal edema 0 – none, 1 – mild, 2 – moderate to severe, 3 – severe, 4 – obstructive	0 (0–1)	0 (0–1)	0	1
posterior commissure hypertrophy 0 – none, 1 – mild, 2 – moderate to severe, 3 – severe, 4 – obstructive	2 (1–2)	1 (1–2)	15	<0,001
granulomas 0 – absent, 2 – present	0 (0–0)	0 (0–0)	2	0,18
thick laryngeal mucus 0 – absent, 2 – present	0 (0–0)	0 (0–0)	0	1
Total RFS	9 (8–10)	6 (5–7)	50	<0,001

timbre [38]. LPR-related morphological changes within the larynx are pleomorphic in nature. Notably, no single typical presentation of larynx was established on the basis of indirect laryngoscopy examinations. LPR may be manifested by acute or chronic laryngitis, laryngitis posterior, interarytenoid fold congestion, arytenoid cartilage swelling, posterior commissure hypertrophy, vocal process edema, contact ulcers, stenosis of Morgagni ventricles, vocal cord nodules, restricted mobility within the cricoarytenoid joint, infraglottic edema (*pseudosulcus*) or infraglottic stenosis and, finally, laryngeal cancer [38]. The most common lesions include redness and swelling of posterior laryngeal segment, mostly limited to arytenoids, possibly accompanied by thickening and dulling of interarytenoid region. In our study, the most common findings included swelling/congestion of posterior laryngeal mucosa, particularly the posterior segments of vocal folds and arytenoid cartilages as well as hypertrophic lesions within the posterior laryngeal commissure.

The pathogenic impact of LPR on the respiratory system is linked to mucous membrane inflammation caused by the hydrochloric acid-pepsin complex which activates neutrophils thus facilitating accumulation of free radicals which in turn may stimulate carcinogenesis. Studies to date suggest that gastroesophageal reflux is an independent risk factor of laryngeal cancer in both long-term smokers and non-smokers [39]. Smoking reduces the lower esophageal sphincter tone, delays stomach emptying and stimulates secretion of hydrochloric acid which may contribute to exacerbation of reflux [40].

The typical symptoms of GERD in LPR patients are rare. According to Ossakow, only 6% of LPR patients present with heartburn as compared to 89% of GERD patients [47]. As reported by Koufman, the incidence of LPR symptoms is distributed as follows: dysphonia or hoarseness in 71% of patients, coughing in 51% of patients, sensation of a foreign body within the throat in 47% of patients, throat clearing in 42% of patients, and hypercalcemia in 35% of patients [16, 17].

Methods for the assessment of LPR-related symptoms include the reflux symptom index (RSI) as proposed by Belafsky et al. and introduced in 2002. As of this day, RSI is a routine diagnostic tool for the detection of this form of reflux disease [14]. Limited applicability of RSI has been pointed out due to the symptoms being non-specific for unambiguous diagnosis of LPR and elimination of other causal factors or, more specifically, to the possibility of healthy individuals presenting with RSI-listed symptoms. Also raised was the problem of poor correlations between the LPR symptoms, clinical presentation of larynx, and esophageal pH tests. On the other hand, RSI facilitates easy diagnosis and monitoring of the disease in the course of the treatment as it is a repeatable and systematic tool for the assessment of clinical symptoms. In our studies, the RSI thresholds were consistent with symptomatic course of the disease and thus suggested the high applicability of the tool. In the study group, regurgitation of gastric contents up into the pharynx was incidental and moderate in severity, thus having no influence on the natural history of LPR. This is confirmed by reports from other authors who pointed out that the natural history of LPR differs from that of typical GERD where regurgitations may constitute the predominant symptom. According to Nowak et al., 100% of LPR patients report hoarseness while only 6% of them complains about heartburn. For the comparison, 89% GERD patients report experiencing heartburn while none of them presents with any signs of hoarseness [3]. Currently, reflux disease is suggested to be the most common cause of laryngitis. Koufman et al. reporter that concomitant reflux was present in as many as 50% of patients reporting with voice disorders [15–17].

Belafsky et al. also developed the reflux finding score (RFS) scale for the staging of laryngeal lesions. The scale is used to assess the

Tab. IV. Comparison of results obtained in individual domains of RFS scale and total score depending on the sex of patients with laryngopharyngeal reflux (N = 51).

	MEN				WOMEN			
VARIABLES	**BEFORE TREATMENT [MEDIAN (25–75%)]**	**AFTER TREATMENT (MEDIAN [25–75%)]**	**IMPROVEMENT (N)**	**P**	**BEFORE TREATMENT [MEDIAN (25–75%)]**	**AFTER TREATMENT [MEDIAN (25–75%)]**	**IMPROVEMENT (N)**	**P**
subglottic edema	0 (0–0)	0 (0–0)	0	1	0 (0–0)	0 (0–0)	0	1
atrial obliteration	0 (0–0)	0 (0–0)	0	1	0 (0–0)	0 (0–0)	0	1
redness/hyperemia	4 (2–4)	2 (2–2)	14	0,001	4 (4–4)	2 (2–2)	21	<0,001
swelling of the vocal folds	2,5 (2–3)	1,5 (1–2)	10	0,005	3 (2–3)	1 (1–2)	23	<0,001
Diffuse laryngeal edema	0 (0–1)	0 (0–1)	0	1	0 (0–0)	0 (0–0)	0	1
posterior commissure hypertrophy	2 (1–2)	1 (1–2)	7	0,018	2 (2–2)	1 (1–2)	11	0,003
granulomas	0 (0–0)	0 (0–0)	0	1	0 (0–0)	0 (0–0)	2	0,18
thick laryngeal mucus	0 (0–0)	0 (0–0)	0	1	0 (0–0)	0 (0–0)	0	1
Total RFS	9 (8–10)	6 (5–6)	17	<0,001	9 (9–10)	6 (5–7)	33	<0,001

most common lesions found in clinical videoendoscopic examinations in LPR patients [6]. The usefulness of both scales in the assessment of LPR signs and symptoms was confirmed in our own studies as well as in the studies by other authors. Nunes et al. [31] assessed the usefulness of RSI and RFS in laryngopharyngeal reflex patients to demonstrate that the use of these tools was associated with low costs and ease of application, and therefore with high practicability. Clinical index values may be used by specialists in their evaluations of the need for further diagnosis and treatment. The study was conducted in 126 patients with suspected LPR; main complaints included cough, foreign body sensation, and hoarseness. The objective of the study was to minimize the number of undiagnosed patients suffering from LPR and to introduce appropriate treatment based on the comparison of RFS and RSI scores into ENT practice. In most patients, both RFS and RSI values were positive, highly repeatable, and confirmed the occurrence of LPR in 94% of cases [31]. Our study confirmed that both scores were at levels warranting the diagnosis of LPR. The values were reduced significantly following the treatment in both male and female patients. Symptoms suggestive of LPR according to their RSI value were also confirmative of the presence of morphological lesions characteristics for LPR within the larynx. RSI and RFS are not considered a substitute for esophageal pH tests which remain the basic diagnostic tool; however, both scores are helpful auxiliaries in the diagnostics of LPR as well as in the monitoring of patients' response to the treatment.

The treatment of LPR is associated with numerous diagnostic as well as therapeutic problems. Patients often report the lack of efficacy of PPI monotherapy. Thus, a search is ongoing for medications and products which would be more effective in reducing the disease symptoms. In recent years, the importance of medications used for supportive treatment of gastroesophageal reflux and laryngopharyngeal reflux disease has been rising continuously. The importance of hyaluronic acid (HA) and its contribution to the healing of mucosal damage, particularly within the larynx, has been highlighted. HA is a glucosaminoglycan complex consisting of glucuronic acid and N-acetylglucosamine disaccharide units; it is present in nearly all human tissues and constitutes, along with elastin and collagen, a structural element of the connective tissue. The largest quantities of HA are found in synovial fluid, hyaline bodies of the eyes, intestinal walls, skin, cartilage, vagina and ovaries as well as the central nervous system. Lower quantities have been measured within the gastrointestinal and respiratory tract mucous membranes. With age, the body levels of hyaluronic acid are depleted [22]. HA is characterized by high molecular weight (up to 107Da); this property impacts appropriate hydration of skin, mucous membranes, ad other tissues in both physiological and inflammatory conditions [19]. HA's specific ability to bind water results from its atypical molecular structure which is also responsible for its rheological properties such as viscosity, plasticity, and elasticity. Hydrophilic properties of the acid and its ability to form an exceptionally plastic gel allow for fast diffusion of compounds and migration of cells. In addition, HA stimulates migration and activity of lymphocytes and other inflammatory mediators as well as the connective tissue cells by means of binding their surface receptors [20, 21]. This is of vital importance not only for the fast-developing tissues, but also for the healing of skin and mucosal injuries. HA was shown to present with anti-inflammatory, anti-exudative, and antioxidative activity along with varied effects on angiogenesis [7, 8]. It plays a significant role in all phases of the process of healing of wounds and injuries to the skin and mucous membranes [22, 23] (Fig. 4.).

No scars are formed in the healing process involving exogenous HA. This is due to the fact that HA molecules stimulate the synthesis of collagen III rather than collagen I which is typical for fibrosis and scarring processes [7, 24]. Clinical studies demonstrated the efficacy and safety of HA in the prevention and treatment of skin and mucous membrane wounds of varied etiology, e.g. in patients with second-degree burns, bed sores, fistulas, patients undergoing radiotherapy, as well as patients with post-traumatic and post-surgical wounds [24, 25]. Used topically, HA accelerates the healing time of small injuries to the skin and the mucous membranes as well as extensive, treatment-resistant wounds. HA develops a protective film on the surface of the mucous membrane to isolate it from adverse external conditions and protect it from extra damage and superinfection. In this way, it prevents the wound being penetrated by microorganisms, thus promoting the healing and ensuring appropriate hydration in between cells. Hyaluronic acid also reduces the feeling of pain caused by damaged tissue integrity and reduces the risk of scarring [26].

Recently, a combination product containing hyaluronic acid and chondroitin sulphate (HA + CS) together with poloxamer 407, has become available for the treatment of extraesophageal reflux

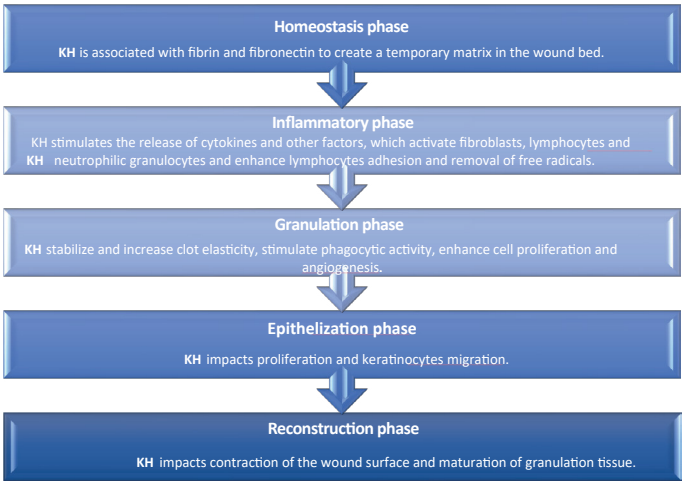

Fig. 4. The role of hyaluronic acid in consecutive phases of wound healing (HA – hyaluronic acid).

disease under the trade name of Esoxx One. In addition to the HA, the product contains chondroitin sulphate (CS), an glucosaminoglycan present naturally in the extracellular matrix which surrounds the cells, particularly within the cartilage, skin, vessels, ligaments, and tendons, where it constitutes an important component of proteoglycans. Chondroitin structure is characterized by 1–3 linkages between D-glucuronic acid and N-acetylgalactosamine molecules. Chondroitin sulphate plays an important biological functions in inflammation as it takes part in the proliferation, differentiation and migration of cells, morphogenesis of tissues, organogenesis, and wound healing process. Its effects are associated with its ability to interact with growth factors, protease inhibitors, cytokines, chemokines, and adhesion molecules. In addition, chondroitin sulfate has immunomodulatory, anti-inflammatory, and antioxidative properties [27]. Another component of Esoxx One, poloxamer 407 (a compound comprised of poly(ethylene oxide) and poly(propylene oxide) blocks), is a hydrophilic, non-ionic surfactant presenting with thermoadhesive properties and used to extend the duration of product's staying in contact with mucous membranes.

Sekino and Murata [41] pointed to radically different levels of glucosaminoglycans, including HA and CS, in esophageal tissues collected at autopsies depending on subject's age. They demonstrated that hyaluronic acid accounted for 62% of all six glucosaminoglycans tested in individuals below the age of 30. A 5-fold reduction in the HA levels was observed in esophageal tissues of patients aged 30 to 60 years, while the levels dropped to as little as 3.5%, i.e. by a factor of almost 18 compared to young subjects, in patients above the age of 60 [41]. One could therefore conclude that the older the patient presenting with reflux and laryngeal lesions, the slower the natural regeneration of the mucous membrane due to the physiological deficiency of HA and the slower the resolution of symptoms. It is particularly in this group of patients where the HA + CS combination delivered on a bioadhesive medium may be of particular therapeutic benefit. However, no appropriate documentation if available as of yet and further studies are required in this aspect.

So far, the efficacy of the new oral HA + CS combination on a bioadhesive medium was the subject of the isolated studies [28–30]. Di Simone et al. [28] performed laboratory experiments with porcine esophageal mucosa to assess the potential barrier effect of Esoxx. Mucosal membrane specimens were subjected to histological staining using the Evans blue dye to assess tissue permeability following chemical damage [HCl, pH 1.47, with or without pepsin (2000 U/mL)]. It was demonstrated that the damage to the mucous membrane of the esophagus was correlated with the perfusion time and the presence of pepsin translating onto mucosal permeability as evidenced by staining experiments. Esoxx reduced the permeability of chemically damaged porcine esophageal mucosa, thus demonstrating a protective effect. The study have confirmed that the HA + CS combination protects the mucous membrane of the GI tract and set up the path for further clinical studies on the treatment of GERD and NERD in humans. Palmieri et al. [29] assessed the impact of the new HA + CS combination in patients presenting with NERD symptoms and poor response to PPI treatment. The study was conducted in a group of 20 patients with NERD confirmed by endoscopic examination of the esophagus, reporting heartburn and/or acid regurgitation on at least 3 days within a 7-day observational period before study inclusion. During the 14-day treatment period, patients received the HA + CS combination in four divided oral doses. The authors observed significant reduction or resolution of NERD symptoms in patients receiving HA + CS as compared to the placebo group, both in relation to heartburn ($P < 0.03$) and to regurgitation of gastric contents to the esophagus ($P < 0.03$). The reported time of the onset of the effect of the oral composition was shorter than 30 minutes in more patients receiving HA + CS compared to the placebo group (60% vs 30%, $P = 0.05$). Total resolution of symptoms was observed in 50% of patients treated with HA + CS as compared to 10% in the placebo group ($P = 0.01$). The HA + CS combination treatment was shown to be effective in controlling gastroesophageal reflux and characterized by prompt onset of the therapeutic effect [29].

Savarino et al. [30] carried out a multicenter, randomized, double-blind study in 154 NERD patients receiving PPI treatment in whom the primary PPI treatment was randomly supplemented with either hyaluronic acid and chondroitin sulphate on bioadhesive medium (Esoxx, Alfa Wassermann, Bologna, Italy) or placebo administered at standard doses over a period of 2 weeks. The objective of the study was to assess whether the combination treatment delivered to protect the mucosa and suppress the secretion of gastric acid (HA + CS and PPI) would reduce symptoms as compared to PPI alone. After 2 weeks, the quality of life as assessed by the patients receiving PPI along with the Esoxx product increased to more closely resemble those in the healthy population. Significant improvement was demonstrated with regard to the reduction of NERD symptoms in patients treated with Esoxx and PPI compared to the groups receiving placebo and PPI. Moreover, tolerance and safety of the tested preparation were high as the total number of adverse events was comparable to that in the placebo group. A synergistic effect was demonstrated for Esoxx and PPI suggesting that mucous membrane protection combined with acid suppression might reduce symptoms and improve the quality of life in NERD patients. The authors underlined the need for further research so as to better assess the impact of the HA + CS combination on esophageal mucosal barrier, particularly

the bioadhesive properties of the product and the duration of its effect [30]. The possibility of use as a rescue medicine, e.g. in order to respond to a dietary mistake and resolve the resulting reflux symptoms, is also an important aspect. Esoxx was demonstrated to be a safe product which is available without prescription and can be used as an alternative to alkalis in self-treatment efforts [29, 30].

Carrasco et al. assessed the efficacy of the HA + CS combination available under the trade name of Ziverel in acute esophagitis caused by radiotherapy (RT) or radiochemotherapy (RT-CH) delivered for lung, esophageal, or gastric cancer in 41 patients. In 38 (92.68%) individuals, reduction in symptoms was observed after 2 weeks of HA + CS combination treatment which completed the primary treatment period. In some patients, the HA + CS combination was used in monotherapy whereas others received the product as a complement to the PPI treatment. The authors concluded that HA + CS was well tolerated and played a key role in the reduction of symptomatic esophagus caused by radiation received as part of cancer treatment [39].

This study is the first one to assess the use of HA + CS combination on bioadhesive medium in patients with laryngopharyngeal reflux. Studies to date focused on the treatment of patients with GERD and NERD [30]. The analysis of RSI data from LPR patients revealed significant improvement in major symptoms such as hoarseness, throat clearing, cough, dysphagia, thick mucus and foreign body sensation within the throat (Tab. I. and II.). The leading symptoms, i.e. throat clearing, hoarseness, and cough after meals/cough when lying down, while being significant or severe at baseline, were reduced to moderate, and thus acceptable by the patient, as the result of the treatment. Baseline morphological lesions indicative of a serious problem (RFS > 7) included erythema/congestion, vocal fold edema, and posterior commissure hypertrophy; these symptoms had been observed in all patients and were significantly reduced as the result of the treatment.

In as many as 40% of NERD patients, resolution of heartburn and/or regurgitation symptoms can't be achieved despite standard or above-standard doses of PPIs being administered [42]. Such a high percentage of failures of PPI monotherapy may be due to LPR being non-acidic or weakly acidic. This was demonstrated in 60 LPR patients in whom weakly acidic reflux was confirmed by esophageal pH tests in 33 cases (55%), non-acidic reflux was confirmed in another 18 cases (30%) while acidic reflux was confirmed in as few as 9 cases (15%) (43). Thus, PPI monotherapy can be insufficient to achieve the desired therapeutic effect; additional protection and PPI being combined with a protective product are probably required in LPR patients. Our research confirms that the HA + CS combination may prove useful in LPR patients as a means to support healing and enhance mucous membrane hydration, particularly within the laryngopharyngeal mucosa. The outcomes of LPR treatment including the use of HA + CS combination were better than those of primary antireflux treatment alone. In terms of symptom reduction, the largest therapeutic benefit was observed in patients in whom previous PPI regimen was supplemented with HA + CS on thermoadhesive medium. The combination is pointed at as the only product which forms a protective layer on the surface of esophageal mucosa thus helping to reduce reflux symptoms and which can be used on a rescue basis either alone or in combination e.g. with proton pump inhibitors.

The study appears to limited by the selected group of patients, all of whom had presented with hoarseness, throat clearing, and cough after meals/cough when lying down. These were the main reasons behind their reporting at the family physician's and at the ENT practice. Hoarseness was the most common symptom responsible for patients being referred for ENT consultations. This was in line with the indication to carry out laryngological consultations in all patients in whom the symptom persists for more than 3 weeks. Prompt referrals for ENT consultations issued by family practitioners to patients presenting with hoarseness to exclude malignancies were of key importance here. LPR may also be a significant everyday obstacle for individuals using their voice as part of their occupation. Another limitation of the study was that only morphological lesions typical for laryngitis posterior were observed in the study material with no other positive symptoms such as extensive laryngeal granulomas, supra- and infraglottic stenoses, or diffuse laryngeal edema. In the study group, morphological lesions observed within the larynx included redness/congestion of the posterior laryngeal segment, swelling of vocal folds and hyperplasia of the posterior commissure; all these lesions were observed in all 51 patients (100%). Posterior commissure hypertrophy was mild to moderate; following the treatment, 18 patients (35.29%) experienced a reduction in the intensity of hypertrophy from moderate (2 points) to mild while the remaining 20 patients (39.21%) experienced no change in the severity of these lesions. Thus, the lesions were rather limited to superficial layers of the mucous membranes representing early pathologies devoid of a significantly proliferative character, i.e. permanent hypertrophy frequently requiring surgical management. Morphological lesions observed in our study were treatable. Thus, it seems that the early stages of the disease are usually more responsive to the treatment. Studies should therefore be extended to increase the probability of demonstrating potential efficacy of HA + CS combination in long-term follow-up. In addition, resolution of symptoms was observed to have preceded the resolution of local lesions, although the latter were subject to gradual regression, too. In these cases, the 2-week treatment period seems to be too short, although it was sufficient to achieve lesion regression in one patient with a granuloma of the vocal process or the right arytenoid cartilage (Fig. 3.). Finally, a question has to be asked: how long should the treatment last? What outcomes can be expected after supportive treatment is discontinued? Patients often reach for supportive treatment and comply with physician's recommendations only when the previously proposed, PPI-based regimen, proves ineffective. In the study group, PPI treatment had been administered to less than half of the patients; it was in this group where the largest therapeutic benefit of the additional protective treatment was observed as manifested by reduction in all reported symptoms.

Notably, hyaluronic acid and chondroitin sulphate combination is recommended by the Polish Society of Family Medicine and the Polish Society of Gastroenterology in their algorithm for the diagnostic and therapeutic management of patients with typical symptoms of gastroesophageal reflux disease or suspected extraesophageal reflux disease [32]. Local effect of the product

on esophageal and upper respiratory tract mucosa is pointed out as the drug promptly and effectively reduces symptoms by providing a protective layer over the mucous membrane and accelerates wound healing and regeneration of esophageal, pharyngeal, and laryngeal epithelium. HA + CS combination is also applicable in the bridging therapy when PPIs and H2-blockers are discontinued 2 weeks before the scheduled diagnostic screening for *Helicobacter pylori.*

For several years, an increasing number of reports on the disturbing phenomenon of unwarranted, chronic misuse of PPIs and harmful effects thereof, have been published in the literature. This pertains to preparations used in a chronic manner as prescribed by physicians of various specialties as well as those available without prescription. The consequences of chronic gastric acid suppression therapies include increased incidence of *Clostridium difficile* infections, small intestine bacterial overgrowth (SIBO), and increased susceptibility to infections caused by pathogens such as *Salmonella spp., Campylobacter jejuni,* and *Escherichia coli* or *Listeria monocytogenes*. Adverse effects of these drugs include vitamin B12 deficiency, drug interactions, gastrointestinal symptoms, constipation or diarrhea, nausea, dizziness and headache, increased activity of liver enzymes, skin eruptions. Proton pump inhibitors misuse rates are estimated at 36–63% of primary care patients and 27–76% of hospitalized patients [30]. In addition, PPIs increase the risk of numerous diseases, such as chronic renal insufficiency, myocardial infarction, pneumonia, bone fractures, enteritis and peritonitis, and dementia [33, 34]. In recent years, GERD was demonstrated to be associated with a greater risk of respiratory tract malignancies including laryngeal cancer, with the odds ratio being increased nearly three times (OR 2.86, 95% CI, 2.65–3.09), as well as with a greater risk of laryngopharyngeal and oropharyngeal cancer (OR 2.54, 95% CI 1.97–3.29) [35]. Cherry et al. were the first to point at the possibility of laryngopharyngeal reflux contributing to the development of laryngeal cancer [36]. Studies are ongoing with regard to LPR's impact on chronic inflammation as well as on the emergence and growth of tumor cells within the larynx. Glanz and Kleinsasser described 35 cases of patients with chronic hypertrophic laryngitis subsequently developing into cancer [40]. Episodes of pathological gastroesophageal reflux are also observed more frequently in laryngeal cancer patients as compared to the control population [37]. Thus, efforts should be all the more directed in the search for novel and more effective methods of GERD treatment.

SUMMARY

By coating the mucous membrane of the larynx and pharynx, the HA + CS combination on a bioadhesive medium ensures its longer-lasting protection against the harmful effects of hydrochloric acid and pepsin as well as accelerates the healing of previously inflamed mucous membrane. HA + CS significantly reduces the LPR-related symptoms, particularly in patients with chronic cough and hoarseness, frequently when administered to support PPI therapy. The product facilitates better hydration of mucous membranes, particularly within the throat and the larynx, promotes healing of mucosal lesions caused by laryngeal reflux, and provides a valuable supplementation to the proton pump inhibitor treatment. It also protects the mucous membrane and is well tolerated by patients as no adverse effects were observed following its use in LPR patients. The product was shown to reduce both main LPR-related symptoms and morphological lesions induced thereby. However, demonstration of product's efficacy in this GERD variant requires the study being extended to a larger group of patients, including patients with more advanced laryngeal lesions, mainly proliferative/hypertrophic lesions, as well as the optimum duration of treatment being determined. The period of 2 weeks as proposed in this study was indicative of a significant reduction in LPR symptoms and partial resolution of lesions caused by the disease. Not studies were conducted in patients following chronic use and then discontinuation of the product. In view of the size of the study group, limited range of morphological lesions within the larynx, lack of chronic use follow-up and limitations associated therewith, the study should be extended and continued.

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