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Research Article

# Treatment of Laryngopharyngeal Reflux Disease Using an Oral Medical Device: A Clinical Investigation into Signs, Symptoms and Quality of Life of Patients

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## Abstract

In recent years, there has been a trend towards the application of alternative therapeutic approaches for the treatment of Laryngopharyngeal reflux (LPR), motivated by the not always satisfactory efficacy of proton pump inhibitors and the risks associated with their long-term use. Based on these premises, this prospective study assesses the results of treating LPR by taking a medical device (MDL) by mouth, aiming to prevent the reflux of gastric contents, and to protect the oesophageal and laryngopharyngeal mucosa. The study was carried out by enlisting 67 subjects divided into two groups: 40 LPR patients were treated for 30 consecutive days with MDL, whilst the other 27 subjects were recruited from the healthy population and used as a healthy control group. Before the start of treatment (T0), at the end of 30 days of treatment (T1) and 30 days after the discontinuation of treatment (T2), symptoms were assessed using the Reflux Symptom Index (RSI), signs were assessed using video laryngoscopy and the Reflux Finding Score (RFS) and health-related quality of life was assessed using the 12-Item Short Form Health Survey (SF-12). At T1, the total RSI and RFS scores improved significantly ($p < 0.0001$) and remained significantly better than before treatment, even after 30 days of stopping MDL treatment ($p < 0.0001$). The thick endolaryngeal mucus sign included in the RFS improved so much that, after 30 days of MDL treatment, the figure was not significantly different from that gathered in healthy subjects ($p = 0.0765$).

Health-related quality of life, as measured by the SF-12 questionnaire, also improved at the end of 30 days of MDL treatment: Physical Component Summary and Mental Component Summary (MCS) index scores improved significantly at T1 ($p < 0.0001$), confirming the improvement in patients' physical and mental state. At T1, the difference between the MCS index score of patients treated with MDL and that of healthy subjects was no longer significant ($p = 0.2015$).

Patients treated with MDL gave a positive assessment of the effectiveness of the medical device at the end of the treatment. The study confirmed the safe use of the product.

**Keywords:** Laryngopharyngeal Reflux; Thick Endolaryngeal Mucus; Magnesium Alginate; *Opuntia ficus-indica* Extract; *Olea europea* Extract; Medical Device

## Abbreviations

LPR: Laryngopharyngeal Reflux; MDL: Tested Medical Device; RSI: Reflux Symptom Index; RFS: Reflux Finding Score; SF-12: 12-Item Short Form Health Survey; PCS: Physical Component Summary; MCS: Mental Component Summary; GERD: Gastroesophageal Reflux Disease; PPIs: Proton Pump Inhibitors; NRS: Numerical Rating Scale; *O. ficus-indica*: *Opuntia ficus-indica*; *O. europaea*: *Olea europaea*

## Introduction

This article presents the results of the processing of the data collected during the clinical trial concerning signs, symptoms and quality of life conducted in patients with reflux disease treated with the tested medical device. The processing and presentation of the results of the rhinocytopathological study conducted in patients with reflux disease treated with the same medical device resulted in a previous publication [1].

In an important study published in 1991, the laryngopharyngeal signs of gastroesophageal reflux disease (GERD) were described and it was pointed out that these signs were often not associated with the characteristic symptoms of GERD [2]. In this study, the authors pointed out that just three weekly episodes of reflux are sufficient to induce severe laryngeal damage, that the main damaging agent in the reflux is pepsin rather than hydrochloric acid and that severe laryngeal damage can be induced by a reflux with a pH of 4.0 [2]. In order to define this characteristic picture of signs and symptoms, with its peculiar aetiopathogenesis, a nosological entity distinct from GERD has been introduced in the scientific literature, which has been given the name of laryngopharyngeal reflux (LPR) [3]. In a recent review, LPR was defined as an inflammatory condition of the tissues of the upper aerodigestive tract relating to the direct and indirect effects of the reflux of gastroduodenal contents, which could induce morphological changes in the upper aerodigestive tract [3]. It could present with a variety of signs and symptoms, including hypopharyngeal globus sensation, chronic dysphonia, raclage, chronic cough, dysphagia, subglottic stenosis, laryngospasm, sinusitis and chronic rhinitis, caused by direct mechanisms such as exposure of the laryngopharynx to hydrochloric acid, pepsin and bile acids, or caused by indirect mechanisms involving laryngeal reflexes evoked by gastric reflux although it does not reach the laryngopharyngeal tissue [3]. Even after a modest number of reflux episodes, damage to the cellular structure of the laryngopharynx was observed in LPR patients, but no damage to the oesophageal mucosa was reported [4].

LPR is common and it is estimated that individuals with LPR-related disorders account for approximately 10%-30% of patients referred to an otolaryngologist [5].

A common practice is to initially treat LPR with acid-suppressing drugs such as proton pump inhibitors (PPIs) [6,7]. Two systematic reviews and meta-analyses have concluded that PPIs are more effective than placebo in the treatment of LPR, but heterogeneity in study designs makes comparisons difficult; therefore, there is still uncertainty regarding how effective PPIs really are in the management of LPR. Furthermore, it has not been established whether one PPI is superior to another in the treatment of LPR [6,7]. It can be assumed that the lack of effective treatment of LPR may explain why patients with LPR or GERD and LPR complain of a lower health-related quality of life than patients with GERD alone [8].

In the past few years, there has been a trend towards the application of alternative therapeutic approaches for the treatment of LPR [9]. This trend has been supported by the not always satisfactory efficacy of PPIs and by the risks associated with their long-term use, including the increased risk of cardiovascular disease, fractures, pneumonia, Clostridium difficile infections, acute and chronic kidney disease, as well as nutritional deficiencies [10]. These risks are exacerbated in the case of LPR, as LPR symptoms require more aggressive and prolonged PPI treatment than in GERD [11,12].

Based on these premises, this prospective study assesses the results of LPR treatment via the oral administration of a medical device designed to prevent the reflux of gastric contents, neutralise the acid pocket that forms near the gastroesophageal junction during meals and protect the oesophageal and laryngopharyngeal mucosa. The aim was to confirm the efficacy of the medical device in performing these actions, on the assumption that the activities of the individual ingredients, in the doses in which they are present in the product, had already been highlighted in the scientific literature. It is assumed that the combination of these ingredients can provide a synergistic action, which is superior to the action of any single ingredient in the treatment of LPR. Therefore, the primary objective of this study was to assess the effectiveness of

the tested medical device in reducing the signs and symptoms of LPR. This is to be achieved both by assessing the improvement in parameters induced by the use of the medical device in LPR patients and by comparing the improved parameters with the same parameters measured in a sample of healthy, non-LPR patients. Secondary objectives are to assess the improvement in quality of life induced by taking the medical device and to assess the effectiveness of the medical device by patients.

## Materials and Methods

### Tested medical device

The tested medical device (MDL, brand name Leniref®, Pharma Line S.r.l. Via Agostino Bertani 2, Milan, Italy - Conformite Europeenne certificate No. 471-00-00 MD, issued on 20 April 2020) is based on magnesium alginate, calcium carbonate, potassium bicarbonate, *Opuntia ficus-indica* L. extract and *Olea europaea* L. extract. The product is indicated for the treatment of gastroesophageal reflux, LPR and associated symptoms. The product was made available free of charge by Pharma Line.

### Study population

The MDL group included adult male and female patients with LPR. To be included, patients had to be over 18 years old, present with symptoms of LPR for at least 3 months and at least 3 times per week, have a Reflux Symptom Index (RSI) score [13] greater than 13 and, on videolaryngoscopy, have morphological lesions of the larynx attributable to LPR, confirmed by a Reflux Finding Score (RFS) [14] greater than 7. Patients were enrolled who had not yet received continuous treatment for LPR, or patients who had already received treatment for LPR. In the latter case, T0 was temporally placed 15 days after the discontinuation of any therapy based on antacids, alginates or other products for the treatment of reflux. Patients already on PPIs continued to take the same daily dose of these drugs throughout the study period.

Subjects with a known sensitivity to one or more components of MDL, malignant or inflammatory diseases of the upper respiratory tract and upper gastrointestinal tract, inhalant or food allergies, as well as pregnant and breastfeeding women were excluded from the study.

In addition, healthy subjects were included for comparison purposes. These subjects had to be over 18 years of age, male or female, have a RSI score of less than 13 and, on videolaryngoscopy, have no morphological lesions of the larynx attributable to LPR, a condition confirmed by an RFS score of less than 7.

Patients were enlisted with their personal identification data and signed a regular informed consent to both the proposed therapy and the processing of personal data. At the time of enrolment, a medical history form was completed for each patient, containing all the data collected and a form to be completed at the next follow-up was attached.

The healthy subjects were enrolled with their personal identification data, signed a regular consent to the processing of personal data and a medical history form was completed for each patient, containing all the data collected during the single examination they underwent.

### Study design

This is a prospective, multi-centre, study comparing LPR patients treated with MDL with healthy subjects.

The period of patient enrolment and treatment was extended from February to August 2021.

Patients in the MDL group were screened on three occasions: at the start of MDL intake (T0), after 30 days of MDL intake (T1) and 30 days after stopping MDL intake (T2). From the time of the start of treatment (T0) and over the following 30 days (T0 to T1), patients took MDL in the amount of one stick pack after each of the two main meals of the day and before going to bed to sleep at night.

Healthy subjects were tested on one occasion (T0).

### Assessment

At the time of enrolment, all subjects underwent an accurate medical history with an assessment of allergies, symptoms, smoking, occupation, family history of respiratory and allergic diseases, operations undertaken and ongoing therapies. An objective examination was also conducted.

Patients in the MDL group at T0, T1 and T2 and healthy subjects at T0 only answered the RSI questions and underwent a videolaryngoscopy, through which the physicians were able to complete the RFS. In addition, patients in the MDL group gave their opinion on the efficacy of MDL therapy at T1 by completing a

numerical rating scale (NRS) in which a value of 0 corresponds to no efficacy and a value of 10 to the highest possible efficacy.

Patients in the MDL group at T0, T1 and T2 and healthy subjects at T0 only completed the 12-Item Short Form Health Survey (SF-12), which has already been used in clinical trials concerning reflux disease [15,16].

Lastly, reports of any adverse effects attributable to taking MDL were collected.

### Statistical analysis

Descriptive statistics were used to summarise the characteristics of the cohorts in terms of median, 25$^{th}$ and 75$^{th}$ percentiles, mean and standard deviation or frequencies, when appropriate.

The effect of MDL treatment was estimated in terms of change in outcomes in the MDL group and in terms of comparison of outcomes between the MDL group and healthy subjects. The significance of the differences was determined by applying the non-parametric Mann-Whitney test for paired data from the MDL group when comparing data at T2, T1 and T0 and for unpaired data when comparing data from the MDL group with healthy subjects. In all the analyses carried out the results are considered statistically significant for $p < 0.05$. Tukey's representation was used for graphs.

The R software version 3.6.1 for Windows (R Core Team; 2013. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) was used for statistical processing.

## Results and Discussion

### Results

Sixty-eight subjects were included in the study, including 41 patients (23 men, 18 women) with LPR and treated with MDL (MDL group) and 27 healthy subjects (12 men, 15 women). Table 1 contains the demographic and medical history data of all subjects included in the study.

On average, T1 is 29.5 ± 2.0 days after T0 and T2 28.5 ± 3.8 days after T1.

One patient did not complete the study intake cycle and was excluded. Analyses were then conducted using data from the remaining 40 patients treated. Within the MDL group, the scores on the questionnaires supplied during the study at T0, T1 and T2 were not influenced by concomitant intake of PPIs, cigarette smoking habits or male or female gender. In fact, no significant differences were found when performing statistical tests.

| Variable | MDL group (n = 41) | Healthy subjects (n = 27) |
|---|---|---|
| Age in years | 52.4 ± 13.1 | 31.6 ± 10.0 |
| Gender, % F (n) | 43.9 (18) | 56.6 (15) |
| Height (cm) | 169.7 ± 7.6 | 169.2 ± 7.2 |
| Weight (kg) | 68.2 ± 13.2 | 64.5 ± 10.7 |
| BMI | 23.6 ± 3.4 | 22.4 ± 2.5 |
| Smoking, % yes (n) | 31.7 (13) | 29.6 (8) |
| Presence of symptoms since (months) | 28.9 ± 46.6 | |
| Days with symptoms per week | 5.6 ± 1.8 | |
| WFI uptake, % yes (n) | 34.1 (14) | |

**Table 1:** Demographic and medical history data of MDL group patients and healthy control subjects. Data are expressed as mean ± SD, unless otherwise stated.

MDL group patients and healthy subjects were asked to rate the intensity of the symptoms listed in the RSI using the following scale: no symptom (0 points), very mild symptom (1 point), mild symptom (2 points), moderate symptom (3 points), severe symptom (4 points), very severe symptom (5 points).

In the MDL group, the total RSI score improved significantly at T1 compared with T0. In the RSI, a score of 13 is the threshold above which the patient is considered to have LPR. After 30 days of treatment with MDL (T1), there is a significant reduction in the RSI score. The median of the total score drops to 8, which is lower than 13. Specifically, at T1, 33 out of 40 patients (82.5%) scored less than or equal to 12. This confirms the significant improvement in LPR symptoms. At T2, 30 days after stopping MDL, the score worsens compared with T1, but remains significantly lower than at T0 (Table 2, Figure 1). At T0, the RSI score of patients in the MDL group is significantly higher than that of healthy subjects. At T1, due to the significant improvement observed in patients in the MDL group, the difference with healthy subjects is reduced but remains significant.

Considering the individual items of the RSI separately, it can be seen that they all undergo a statistically highly significant reduction from T0 to T1 (Table 2). At T2, the score worsens slightly but remains significantly lower than at T0 for all items. In addition, it can be seen that, at T0, T1 and T2, the scores of the MDL group are always significantly higher than those of the healthy subjects.

| Item RSI | Parameters | Healthy subjects | Treated patients (Group MDL; n = 40) | | |
|---|---|---|---|---|---|
| | | | T0 | T1 | T2 |
| Total | Median [25° - 75°] | 2.00 [1.00 - 3.00] | 20.00 [17.00 - 23.00] | 8.00 [7.00 - 10.00] | 10.00 [9.00 - 12.75] |
| | P-value vs healthy subj. | | < 0.0001 | < 0.0001 | < 0.0001 |
| | P-value vs T0 | | | < 0.0001 | < 0.0001 |
| 1 - Hoarseness or a problem with your voice | Median [25° - 75°] | 0.00 [0.00 - 1.00] | 2.00 [1.00 - 3.00] | 1.00 [0.00 - 1.00] | 1.00 [1.00 - 2.00] |
| | P-value vs healthy subj. | | < 0.0001 | 0.0024 | < 0.0001 |
| | P-value vs T0 | | | < 0.0001 | < 0.0001 |
| 2 - Clearing your throat | Median [25° - 75°] | 0.00 [0.00 - 1.00] | 3.00 [2.00 - 3.00] | 1.00 [1.00 - 2.00] | 2.00 [1.00 - 2.00] |
| | P-value vs healthy subj. | | < 0.0001 | 0.0002 | < 0.0001 |
| | P-value vs T0 | | | < 0.0001 | < 0.0001 |
| 3 - Excess throat mucus or postnasal drip | Median [25° - 75°] | 0.00 [0.00 - 1.00] | 4.00 [3.00 - 4.00] | 2.00 [1.00 - 2.00] | 2.00 [1.00 - 3.00] |
| | P-value vs healthy subj. | | < 0.0001 | < 0.0001 | < 0.0001 |
| | P-value vs T0 | | | < 0.0001 | < 0.0001 |
| 4 - Difficulty swallowing food, liquids, or pills | Median [25° - 75°] | 0.00 [0.00 - 0.00] | 1.00 [0.00 - 2.00] | 0.00 [0.00 - 1.00] | 0.00 [0.00 - 1.00] |
| | P-value vs healthy subj. | | < 0.0001 | 0.0004 | < 0.0001 |
| | P-value vs T0 | | | < 0.0001 | 0.0004 |
| 5 - Coughing after you ate or after lying down | Median [25° - 75°] | 0.00 [0.00 - 0.00] | 1.50 [1.00 - 3.00] | 0.00 [0.00 - 1.00] | 1.00 [0.00 - 2.00] |
| | P-value vs healthy subj. | | < 0.0001 | < 0.0001 | < 0.0001 |
| | P-value vs T0 | | | < 0.0001 | < 0.0001 |
| 6 - Breathing difficulties or choking episodes | Median [25° - 75°] | 0.00 [0.00 - 0.00] | 1.00 [0.00 - 1.00] | 0.00 [0.00 - 0.00] | 0.00 [0.00 - 1.00] |
| | P-value vs healthy subj. | | < 0.0001 | 0.0176 | 0.0004 |
| | P-value vs T0 | | | < 0.0001 | 0.0005 |

| | | | | | |
|---|---|---|---|---|---|
| 7 - Troublesome or annoying cough | Median [25° - 75°] | 0.00 [0.00 - 1.00] | 3.00 [2.00 - 3.75] | 1.00 [0.00 - 1.75] | 1.00 [0.00 - 2.00] |
| | P-value vs healthy subj. | | < 0.0001 | 0.0024 | 0.0002 |
| | P-value vs T0 | | | < 0.0001 | < 0.0001 |
| 8 - Sensations of something sticking in your throat or a lump in your throat | Median [25° - 75°] | 0.00 [0.00 - 1.00] | 2.50 [2.00 - 3.75] | 1.00 [0.00 - 1.75] | 1.00 [1.00 - 2.00] |
| | P-value vs healthy subj. | | < 0.0001 | 0.0006 | < 0.0001 |
| | P-value vs T0 | | | < 0.0001 | < 0.0001 |
| 9 - Heartburn, chest pain, indigestion, or stomach acid coming up | Median [25° - 75°] | 0.00 [0.00 - 0.00] | 3.00 [2.00 - 4.00] | 1.00 [1.00 - 2.00] | 1.00 [0.25 - 2.00] |
| | P-value vs healthy subj. | | < 0.0001 | < 0.0001 | < 0.0001 |
| | P-value vs T0 | | | < 0.0001 | < 0.0001 |

**Table 2:** Medians of the total RSI score and the score of individual RSI items found in healthy subjects and in the MDL Group at T0, T1 and T2, as well as statistical significance of comparisons.

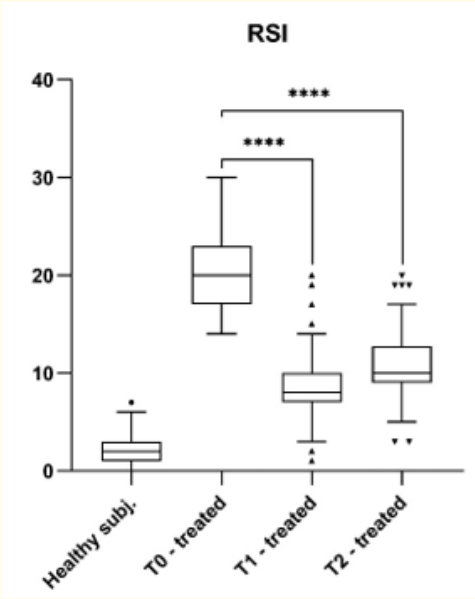


**Figure 1:** Treatment with MDL for 30 days (T1) resulted in a significant reduction in the RSI score, which remained significantly lower than the value at T0 even 30 days after stopping therapy (T2) (****p < 0.0001). The RSI score in the MDL group was always significantly higher than in healthy subjects.

Of the symptoms detected by the RSI, four were on average more severe at T0. The scores attributed to these symptoms at T0 and the results after 30 days of MDL intake and 30 days after discontinuation of MDL intake are summarised in table 3.

| Item RSI | Score | MDL Group patients affected by the symptom (% (n); tot. no. = 40) | | |
|---|---|---|---|---|
| | | T0 | T1 | T2 |
| Excess throat mucus or postnasal drip | 5 | 15% (6) | 2.5% (1) | 2.5% (1) |
| | 4 | 47.5% (19) | 2.5% (1) | 2.5% (1) |
| | 3 | 20% (8) | 12.5% (5) | 22.5% (9) |
| | 2 | 7.5% (3) | 40% (16) | 42.5% (17) |
| | 1 | 7.5 % (3) | 30% (12) | 22.5% (9) |
| | 0 | 2.5% (1) | 12.5% (5) | 7.5% (3) |
| Heartburn, chest pain, indigestion, or stomach acid coming up | 5 | 5% (2) | 0% (0) | 0% (0) |
| | 4 | 32.5% (13) | 2.5% (1) | 5% (2) |
| | 3 | 17.5% (7) | 5% (2) | 2.5% (1) |
| | 2 | 30% (12) | 27.5% (11) | 35% (14) |
| | 1 | 5% (2) | 42.5% (17) | 32.5% (13) |
| | 0 | 10% (4) | 22.5% (9) | 25% (10) |
| Troublesome or annoying cough | 5 | 5% (2) | 2.5% (1) | 2.5% (1) |
| | 4 | 20% (8) | 2.5% (1) | 2.5% (1) |
| | 3 | 37.5% (15) | 0% (0) | 5% (2) |
| | 2 | 30% (12) | 20% (8) | 25% (10) |
| | 1 | 7.5% (3) | 40% (16) | 35% (14) |
| | 0 | 0% (0) | 35% (14) | 30% (12) |

| | | | | |
|---|---|---|---|---|
| Clearing your throat | 5 | 5% (2) | 2.5% (1) | 2.5% (1) |
| | 4 | 5% (2) | 5% (2) | 5% (2) |
| | 3 | 42.5% (17) | 7.5% (3) | 12.5% (5) |
| | 2 | 37.5% (15) | 20% (8) | 37.5% (15) |
| | 1 | 7.5% (3) | 47.5% (19) | 32.5% (13) |
| | 0 | 2.5% (1) | 17.5% (7) | 10% (4) |

**Table 3:** RSI symptoms perceived with the greatest intensity by patients in the MDL group before MDL treatment (T0) and their course after 30 days of treatment (T1) and after 30 days of treatment discontinuation (T2).

In the MDL group, the total RFS score improved significantly at T1 compared with T0. In the RFS, a score of 7 is the threshold above which the patient is considered to have LPR. After 30 days of treatment with MDL (T1), there is a significant reduction in the RFS score. The median of the total score drops to 8. Specifically, at T1, 18 out of 40 patients (45%) scored less than or equal to 7. This confirms the significant improvement in the signs presented by the patients. At T2, 30 days after stopping MDL treatment, the score worsens compared to T1, but remains significantly lower than at T0 (Table 4, Figure 2). At T0, the RFS score of patients in the MDL group is significantly higher than that of healthy subjects. At T1, due to the significant improvement observed in patients in the MDL group, the difference between them and healthy subjects is reduced but remains significant.

Considering the individual items of the RFS separately (Table 4) it can be seen that subglottic oedema is present in 6 patients of the MDL group at T0, whilst in the remaining 34 patients of the same group it is absent. The consequence of this is that the difference in this sign between the MDL group and healthy subjects is not statistically significant even at T0. After 30 days of treatment with MDL, this sign remains in one patient.

In all patients in the MDL group, there is partial ventricular obliteration at T0 and this situation remains unchanged at T1 and T2, therefore the statistical comparison is meaningless.

82.5% of patients in the MDL group had widespread erythema/hyperemia at T0 and 17.5% had it only at the arytenoid level. After 30 days of MDL treatment (T1), only 10% of patients have this widespread sign, whilst 90% have it only at the arytenoid level.

Vocal fold oedema, diffuse laryngeal oedema and posterior commissure hypertrophy are assessed using a 4-point scale. To show the results of MDL treatment on these signs, the data have been summarised in table 5.

Thick endolaryngeal mucus is present at T0 in 80% of patients in the MDL group. At T1, the percentage drops to 12.5% and the improvement achieved means that the figure at T1 is not significantly different from that collected in healthy subjects (p = 0.0765).

Granuloma/granulation tissue are absent in all patients in the MDL group already at T0.

| Items RFS | Parameters | Healthy subjects (n = 27) | Patients treated (MDL group; n = 40) | | |
|---|---|---|---|---|---|
| | | | T0 | T1 | T2 |
| Total | Median [25° - 75°] | 0.00 [0.00 - 3.00] | 13.00 [12.00 - 14.00] | 8.00 [7.00 - 9.00] | 9.00 [8.00 - 10.00] |
| | P-value vs healthy subj. | | < 0.0001 | < 0.0001 | < 0.0001 |
| | P-value vs T0 | | | < 0.0001 | < 0.0001 |
| Subglottic oedema | Median [25° - 75°] | 0.00 [0.00 - 0.00] | 0.00 [0.00 - 0.00] | 0.00 [0.00 - 0.00] | 0.00 [0.00 - 0.00] |
| | P-value vs healthy subj. | | 0.0738 | >0.9999 | 0.2673 |
| | P-value vs T0 | | | 0.0625 | 0.3750 |

| | | | | | |
|---|---|---|---|---|---|
| Ventricular obliteration | Median [25° - 75°] | 0.00 [0.00 - 0.00] | 2.00 [2.00 - 2.00] | 2.00 [2.00 - 2.00] | 2.00 [2.00 - 2.00] |
| | P-value vs healthy subj. | | < 0.0001 | < 0.0001 | < 0.0001 |
| | P-value vs T0 | | | - | - |
| Erythema/hyperaemia | Median [25° - 75°] | 0.00 [0.00 - 0.00] | 4.00 [4.00 - 4.00] | 2.00 [2.00 - 2.00] | 2.00 [2.00 - 2.00] |
| | P-value vs healthy subj. | | < 0.0001 | < 0.0001 | < 0.0001 |
| | P-value vs T0 | | | < 0.0001 | < 0.0001 |
| Vocal fold oedema | Median [25° - 75°] | 0.00 [0.00 - 0.00] | 2.00 [1.00 - 2.00] | 1.00 [1.00 - 1.00] | 2.00 [1.00 - 2.00] |
| | P-value vs healthy subj. | | < 0.0001 | < 0.0001 | < 0.0001 |
| | P-value vs T0 | | | < 0.0001 | 0.0654 |
| Widespread laryngeal oedema | Median [25° - 75°] | 0.00 [0.00 - 0.00] | 2.00 [1.00 - 2.00] | 1.00 [1.00 - 1.00] | 1.00 [1.00 - 2.00] |
| | P-value vs healthy subj. | | < 0.0001 | < 0.0001 | < 0.0001 |
| | P-value vs T0 | | | < 0.0001 | 0.0065 |
| Posterior commissure hypertrophy | Median [25° - 75°] | 0.00 [0.00 - 0.00] | 2.00 [2.00 - 2.00] | 1.00 [1.00 - 2.00] | 1.50 [1.00 - 2.00] |
| | P-value vs healthy subj. | | < 0.0001 | < 0.0001 | < 0.0001 |
| | P-value vs T0 | | | < 0.0001 | < 0.0001 |
| Granuloma/granulation tissue | Absent sign in all patients in MDL group | | | | |
| Thick endolaryngeal mucus | Median [25° - 75°] | 0.00 [0.00 - 0.00] | 2.00 [2.00 - 2.00] | 0.00 [0.00 - 0.00] | 0.00 [0.00 - 0.00] |
| | P-value vs healthy subj. | | < 0.0001 | 0.0765 | 0.0361 |
| | P-value vs T0 | | | < 0.0001 | < 0.0001 |

**Table 4:** Median RFS found in healthy subjects and in the MDL group at the start of therapy (T0), after 30 days of therapy (T1) and after 30 days of discontinuation of therapy (T2) and statistical significance of comparisons. After 30 days of MDL treatment, there was no significant difference between patients in the MDL group and healthy subjects with regard to thick endothelial mucus (p = 0.0765).

| **Item RFS** | **Score** | **MDL group patients showing the sign (% (n); tot. no. = 40)** | | |
|---|---|---|---|---|
| | | **T0** | **T1** | **T2** |
| Vocal fold oedema | 4 (polypoid) | 0% (0) | 0% (0) | 0% (0) |
| | 3 (severe) | 2.5% (1) | 0% (0) | 2.5% (1) |
| | 2 (moderate) | 70% (28) | 12.5% (5) | 52.5% (21) |
| | 1 (mild) | 27.5% (11) | 87.5% (35) | 45% (18) |

| | | | | |
|---|---|---|---|---|
| Widespread laryngeal oedema | 4 (obstructing) | 0% (0) | 0% (0) | 0% (0) |
| | 3 (severe) | 10% (4) | 0% (0) | 0% (0) |
| | 2 (moderate) | 45% (18) | 10% (4) | 32.5% (13) |
| | 1 (mild) | 45% (18) | 90% (36) | 67.5% (27) |
| Posterior commissure hypertrophy | 4 (obstructing) | 0% (0) | 0% (0) | 0% (0) |
| | 3 (severe) | 20% (8) | 0% (0) | 2.5% (1) |
| | 2 (moderate) | 62.5% (25) | 27.5% (11) | 47.5% (19) |
| | 1 (mild) | 17.5% (7) | 72.5% (29) | 50% (20) |

**Table 5:** RFS signs assessed by 4-point scale of MDL Group patients before MDL treatment (T0) and their evolution after 30 days of MDL treatment (T1) and after 30 days of MDL treatment discontinuation (T2).

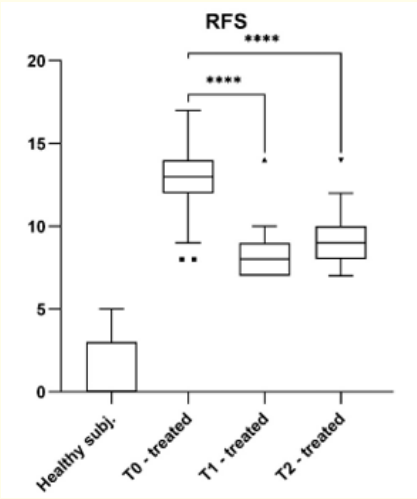


**Figure 2:** Treatment with MDL for 30 days (T1) resulted in a significant reduction in the RFS score, which remained significantly lower than the value at T0 even 30 days after stopping therapy (T2) (****$p < 0.0001$). The RFS score in the MDL group was always significantly higher than in healthy subjects.

The assessment of the results of the SF-12 questionnaire was carried out by dividing the questionnaire into two indices called Physical Component Summary (PCS) and Mental Component Summary (MCS).

The PCS index relates to the physical state of the patient and groups 6 of the 12 questions of the SF-12 questionnaire referring to different areas: two questions concern physical activity, two concern work engagement and physical health, one question concerns physical pain and one concerns general health.

In the MDL group, the PCS index score improved significantly at T1 compared with T0, confirming the improvement in the physical state of the patients. The score worsens at T2, one month after stopping MDL, compared with T1, but remains significantly better than at T0 (Table 6, Figure 3A). At T0, the PCS index score of LPR patients is significantly lower than that of healthy subjects. Despite the significant improvement observed in MDL-treated patients, at T1, the difference with healthy subjects remained statistically significant.

The MCS index measures the mental state of the patient and groups together 6 of the 12 questions of the SF12 questionnaire referring to various areas: one question is about vitality, one about social activities, two are about emotional state and, lastly, two questions refer to mental health.

In the MDL group, the MCS index score improved significantly at T1 compared with T0 confirming the improvement in the mental state of the patients. The score worsens at T2, one month after stopping MDL, compared with T1, but remains significantly better than at T0 (Table 6, Figure 3B). At T0, the MCS index score of LPR patients is significantly lower than that of healthy subjects. Due to the improvement observed after 30 days of MDL treatment, there was no longer a statistically significant difference at T1 between the MCS index score of the MDL group and the MCS index score of the healthy subjects ($p = 0.2015$).

After 30 days of therapy (T1), MDL-treated patients rated the effectiveness of therapy using a VAS scale numbered 0-10. The average rating was 7.13 ± 1.18.

| SF -12 | Parameters | Healthy subjects (n = 27) | Treated patients (n = 40) | | |
|---|---|---|---|---|---|
| | | | T0 | T1 | T2 |
| SF-12 - PCS | Median [25° - 75°] | 54.89 [51.03 - 56.48] | 41.56 [36.04 - 51.25] | 51.10 [47.93 - 53.31] | 48.73 [42.72 - 52.12] |
| | P-value vs healthy subj. | | < 0.0001 | 0.0005 | < 0.0001 |
| | P-value vs T0 | | | < 0.0001 | 0.0011 |
| SF-12 - MCS | Median [25° - 75°] | 53.05 [51.06 - 55.59] | 39.93 [36.37 - 52.98] | 50.49 [46.51 - 55.32] | 46.38 [40.33 - 55.10] |
| | P-value vs healthy subj. | | 0.0043 | 0.2015 | 0.0261 |
| | P-value vs T0 | | | < 0.0001 | 0.0010 |

**Table 6:** Median, 25th and 75th percentiles of the PCS index and MCS index found in healthy subjects and in the MDL group at the start of therapy (T0), after 30 days of therapy (T1) and after 30 days of discontinuation of therapy (T2) and statistical significance of the comparisons. After 30 days of therapy, there was no significant difference between the MCS index score in the MDL group and healthy subjects (p = 0,2015).

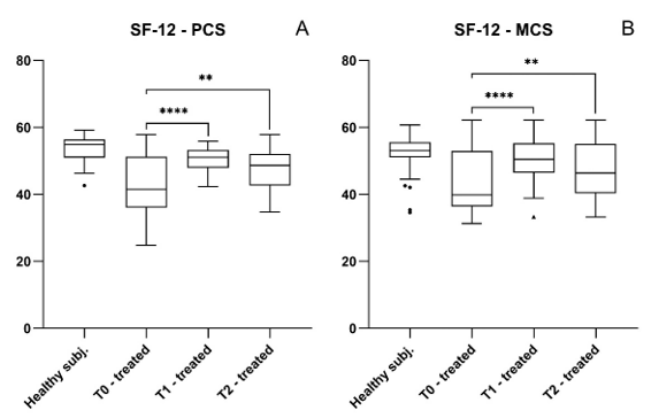


**Figure 3:** MDL treatment for 30 days (T1) resulted in a significant increase in the PCS index score (A) and MCS index score (B), which remained significantly higher than the score at T0 even 30 days after stopping therapy (T2) (****p < 0.0001; **p = 0.0011 for PCS index and **p = 0.0010 for MCS index). The PCS index score in the MDL group was always significantly lower than in the healthy subjects, whilst at T1, the difference between the MCS index scores in the MDL group and in the healthy subjects was not statistically significant (p = 0.2015).

One patient treated with MDL complained of epigastralgia 8 days after starting the product and discontinued treatment.

## Discussion

After 30 days of MDL treatment, the total RSI and RFS scores improved significantly. 33 out of 40 patients (82.5%) had an RSI score less than or equal to 12, which is below the threshold value that may contribute to the diagnosis of LPR and 18 out of 40 patients (45%) had an RFS score of less than or equal to 7, the threshold value for the diagnosis of LPR. Considering the individual items of the RSI and RFS separately, it can be seen that they undergo a statistically highly significant reduction from T0 to T1. The combination of these two observations confirms that treatment with MDL allows for a significant improvement in the signs and symptoms of LPR that patients presented at T0.

30 days after stopping MDL treatment (T2), the total score and the score of the individual items of the RSI worsened compared to T1, but remained significantly lower than the scores at T0. These observations confirm that the therapeutic result obtained over 30 days of treatment with MDL is maintained 30 days after stopping treatment.

Further information can be derived from the comparison between MDL-treated patients and healthy subjects: at T0, both the total score and the scores of the individual RSI and RFS items of the MDL group patients are, in almost all cases, significantly higher than that of the healthy subjects and at T1, thanks to the significant improvement in symptoms and signs in the MDL-treated patients, the difference compared with the healthy subjects

is reduced but remains significant in almost all cases. An exception is thick endolaryngeal mucus, a sign that undergoes such a marked improvement after 30 days of MDL treatment that the figure at T1 is not significantly different from that collected in healthy subjects.

All these observations may suggest that, in order to achieve resolution of the signs, with the exception of thick endolaryngeal mucus which resolved within 30 days of treatment and of the symptoms of LPR as measured by RFS and RSI and to stabilise the result achieved, it is desirable to continue treatment with MDL for longer than 30 days.

Assessments of health-related quality of life, as measured by the SF-12 questionnaire, are in agreement with what has been observed regarding LPR signs and symptoms: PCS and MCS index scores improved significantly at T1 compared with T0 in the MDL group, confirming the improvement in the physical and mental state of patients after 30 days of MDL treatment. Scores worsened at T2, 30 days after stopping MDL, but remained significantly better than at T0, confirming that the results acquired during treatment are maintained within 30 days of stopping treatment. The comparison with healthy subjects is useful: at T0, the PCS and MCS index scores of patients in the MDL group are significantly lower than those of healthy subjects. At T1, the difference with respect to healthy subjects remained statistically significant as regards the PCS index, whereas, as regards the MCS index, there was no longer a statistically significant difference.

The marked improvement in physical and mental state is confirmed by the MDL-treated patients' assessment of the effectiveness of the medical device. Patients considered the therapy to be effective as they scored on average more than 7 on an NRS numbered from 0 to 10. The study also shows that the product under study is safe and well tolerated.

The hypothesis formulated in the introduction seems to be confirmed by the results of the study: treatment with MDL, which aims to prevent the reflux of gastric contents, neutralise the acid pocket that forms near the gastroesophageal junction during meals and protect the oesophageal and laryngopharyngeal mucosa, significantly reduces the signs and symptoms of LPR and improves the quality of life of patients with LPR. This is achieved by the combination of ingredients in MDL's composition, which inhibit inflammation and the accumulation of free radicals in the mucosa that are at the root of LPR's negative impact on the respiratory tract mucosa.

Magnesium alginate and the alkalising substances have a physical action on the gastric level: the reaction that occurs when these substances come into contact with the acidic gastric contents causes the formation of a floating 'raft' that impedes the reflux of the gastric contents into the oesophagus. Alkalising substances react with hydrochloric acid and neutralise the acid pocket formed during a meal. The combination of these actions allows for the effective management of MRGE and LPR symptoms as evidenced in published clinical studies [17-20].

In MDL, a further contribution comes from the therapeutic action directly exerted by the combination of *O. ficus-indica* and *O. europaea* extracts. Studies using animal models document the benefits of using the cladode extract of *O. ficus-indica* and the leaf extract of *O. europaea* in the treatment of disorders of the upper gastrointestinal tract [21-25]. Studies on the therapeutic properties of *O. ficus-indica* extract have demonstrated antiulcerogenic activity, likely due to the mucilages it contains, mainly consisting of arabinogalactan and galacturonic acid, which form a protective layer on the mucous membranes [22,26]. The mucilages of *O. ficus-indica* are highly viscous and bioadhesive and their volume increases on contact with aqueous solutions. These characteristics are thought to be responsible for the protective action of *O. ficus-indica* extract on mucous membranes [26].

*O. europaea* leaf extract contains bioactive compounds with antioxidant and anti-inflammatory activity and is traditionally used for therapeutic purposes in Europe and the Mediterranean basin [27]. Published studies show that aqueous extracts of *O. europaea* are capable of exerting anti-inflammatory action, measured by reducing TNF-α levels in an in vivo experimental model and in an in vitro experimental model on a human lymphocyte cell line [28]. In an in vivo experimental model, it has been shown that the administration of olive leaf extract can prevent the formation of stress-induced gastric lesions [24]. Indeed, olive leaf extract has antioxidant and anti-inflammatory properties that are attributed to bioactive flavonoids and other substances that have been identified in it [29-31].

Lastly, the mucoprotective effect, due to bioadhesiveness and anti-inflammatory action, exerted by the combination of *O. ficus-indica* cladode extract and *O. europaea* leaf extract has been shown in in vitro models simulating in vivo conditions [32].

A novel aspect of this study is the comparison of LPR patients treated with MDL with healthy subjects. The comparison between the patients' status before and after treatment is often considered sufficient. If therapy is carried out with substances that have already proven to be active in treating the disorder in question, significant improvement in the parameters selected for clinical assessment can be easily achieved. This type of result does not enable an assessment to what extent the improvement achieved brings the state of patients at the end of treatment closer to the state of healthy subjects. Thus, the comparison of treated patients with healthy subjects in this study is intended to at least partially obviate this potential bias in testing the effectiveness of therapy and is intended to help determine how long treatment should be continued to achieve the best results.

A limitation of this study may be the lack of a control arm consisting of LPR patients treated with placebo. The authors of this study did not consider this necessary, primarily because alginates combined with alkalinising substances and the combination of *O. ficus-indica* and *O. europaea* extracts have already been tested in clinical trials versus placebo in the treatment of GERD or in clinical trials versus PPIs in the treatment of LPR. Thus, the individual ingredients of MDL have a history of testing that confirms their efficacy [20,33,34]. Furthermore, this study was carried out in the context of the authors' usual clinical activity. The authors did not consider it ethically correct to treat patients who came to them with the intention of resolving the disorder they were suffering from by means of placebo therapy.

## Conclusion

In this study, we show the improvement of all evaluated parameters after 30 consecutive days of MDL intake by LPR patients. In fact, symptoms and signs of LPR, assessed by RSI and RFS respectively, improved significantly with treatment. The 30 days of treatment were sufficient to reduce the thick endolaryngeal mucus sign so markedly that the data at T1 were not significantly different from those collected in healthy subjects. The study shows an improvement in health-related quality of life: scores on the PCS index, which relates to the patient's physical state and the MCS index, which relates to the patient's mental state, improved significantly at T1 compared with T0 in the treated patients, confirming the improvement in the patients' physical and mental state after 30 days of MDL treatment. The 30 days of treatment were sufficient to return the patients to a mental state (MCS index) comparable to that of healthy subjects. The tolerability of the medical device was good and the results were considered more than satisfactory by the patients treated. The results of this clinical study thus demonstrate the efficacy of MDL, comprising magnesium alginate, calcium carbonate, potassium bicarbonate and extracts of *O. ficus-indica* and *O. europaea*, in reducing the signs and symptoms commonly associated with LPR and improving the quality of life of LPR patients. The study also shows that the product under study is safe and well tolerated.

Further clinical studies are desirable to further increase the evidence of MDL efficacy and to determine the most appropriate time extension of treatment cycles.

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## Conflict of Interest

The authors declare that they have no commercial associations that might pose a conflict of interest in connection with the submitted article.

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