**Project Protocol**

Title

The efficacy of Larri® Oral Spray in the management of pepsin salivary test positive Laryngopharyngeal reflux disease.

Version 1, 17/01/2022

Project Team Roles & Responsibilities

Paul Paddle – Principal investigator, ENT Surgeon at Monash Health

Roles: supervision, project conceptualisation, project monitoring, manuscript writing.

Mostafa Alwan – Co-investigator, ENT Registrar at Monash Health

Roles: Ethics submission, data collection and analysis, manuscript writing.

Claire Stanley – Co-investigator, Speech pathologist at Monash Health

Roles: Participant recruitment, Data collection, test analysis.

Anthony Rotman – Co-investigator, ENT Surgeon at Monash Health

Roles: Participant recruitment, Manuscript writing

Background

Larri® Oral Spray is a newly released over-the-counter product in the Australian market, which contains Magnesium Alginate, Sodium Hyaluronate and Camellia Sinensis, and is marketed as a treatment of the symptoms associated with Laryngopharyngeal Reflux (LPR) and Gastro-Oesophageal Reflux Disease (GORD).

Being a newly released product there are currently no randomised control trials demonstrating the efficacy of this medication and testing its therapeutic claims. However, mechanistically, with the contained active ingredients, its efficacy does hold promise, and may be a useful adjunct to current available treatments(1).

Aims/Objectives

To test the efficacy of Larri® Oral Spray in the management of LPR/GORD as measured by a change in the reflux symptom index (RSI), in patients with a Clinical and Oral Salivary pepsin positive diagnosis of LPR.

Expected outcomes

We anticipate that there will be a measurable modest effect in patient symptoms for those who are commenced on Larri Oral Spray when compared to a placebo.

Project Design

*Research Project Setting*

This project will be based at Moorabbin Hospital through Monash Health. Patients will be recruited from Monash Health laryngology clinics, and Melbourne Voice analysis centre private clinics (MVAC). A further public participant recruitment process through social media channels may also be developed, depending on success of initial direct patient recruitment measures.

*Methodological approach*

Given that we are testing a new product aimed at the treatment of LPR, we have determined that the most appropriate and robust method to assess the efficacy of this product is a randomised control trial whereby the product is directly compared to a placebo product.

*Participants*

We aim to recruit a total of 80 patients with LPR, 40 in each arm (Larri Oral Spray and placebo spray). This sample size was arrived at based on our power calculations and anticipated effect size and out budget (please see below).

*Approaches to provision of information to participants and consent*

Potential prospective participants will be approached by their laryngologist during a clinical consultation and verbal and written consent will be sought. Participants will be provided with a detailed consent form and given a number to contact in the event of any desire to re-negotiate consent or to withdraw from the study.

*Research Activities*

To qualify for this study, participants must be clinically suspected of suffering from LPR (on history and/or endoscopy) by a laryngologist/speech pathologist, and demonstrate pepsin positivity on at least 1 of 3 Peptest® samples (i.e. a standard 24-hour oral salivary pepsin test). Peptest® is a commercially available Immuno-assay which qualitatively and quantitatively assess for the presence of pepsin in a patient’s saliva. The Peptest® will be analysed locally, using established protocols/standards. Peptest® has recently been demonstrated to be a reliable method in confirming the presence of reflux in patients who have clinical symptoms of LPR/GERD(2). A recent literature review and metanalysis has demonstrated a pooled sensitivity of 62% (95% CI 49-73%) and specificity of 74% (95% CI 50-90%)(3).

Recruited subjects will then **subsequently** be administered a baseline Reflux Severity Index (RSI), and Vocal Tract Discomfort Score (VTDS) and provided a standardised, standard of care anti-LPR diet and lifestyle intervention advice. Subjects will also be blindly randomised to receive either Larri® Oral Spray, or a placebo spray. Both arms will be instructed to administer two sprays, four times a day (after breakfast, lunch, and dinner, and before bed).

Participants who are already taking anti-reflux medications will be allowed to continue their current treatment, as we aim to see whether the addition of Larri® Oral Spray provides added benefits to patients who are already receiving the current standard of care. We aim to do a subgroup analysis after this study is completed to answer the following questions:

1. Does the addition of Larri® Oral Spray to current standard of care (Proton pump inhibitor plus an H2 receptor antagonist) provide added symptom benefit?
2. Does Larri® Oral Spray used as monotherapy have statistically and clinically significant symptom benefit when compared to a placebo?

After eight weeks of treatment, participants will be asked to complete a secondary RSI, and the results will be recorded.

*Sample size and statistical power*

We have anticipated a difference in score between the intervention and control group of 5 points on the RSI questionnaire. Using a difference of 5, an alpha of 0.05 and a power of 0.8, we anticipate that we will require 10 patients in each arm to detect this difference However in order to increase the power of our study and anticipate patient non-compliance or discontinuation from the trial, as well due to realistic budget constraints, we will be aiming to recruit 40 patients in each arm of the study.

Previous studies have demonstrated that oral proton pump inhibitors resulted in an improvement in patients’ RSI score of 10(1), and therefore we have chosen an RSI score improvement of 5 in our power calculation in order to detect more subtle improvements by increasing the power of our study through recruitment numbers.

*Data Collection*

We will be collecting the following data:

Patient age, sex, BMI, height, weight, smoking status, alcohol intake, past medical history, reflux questionnaire scores before treatment and again after treatment.

*Data Management*

Data will be securely stored in an online password protected encrypted server. Only the investigators will have access to this data, and it will be stored in accordance with Monash Health research and data storage policy for seven years and then securely destroyed.

Patient identity will be coded with a code sheet also stored on the secure server. This will enable investigators to remove patients from the trial who have withdrawn their consent

partway through the study.

*Data Analysis*

We will aim to match patients in the control arm and active arm based on age, sex, smoking history, alcohol history and medical history. This will hopefully eliminate confounding factors. Participants and investigators will be blinded as to which participant is in which arm (double-blind standard trial).

We will attempt to make sure all participants are compliant with their medication or placebo, and endeavour to ensure all participants answer their post-treatment reflux questionnaire, however some loss of participation is anticipated and inevitable. To account for this, our sample size is larger than we initially estimated we would need from our power calculation.

Statistical analysis will be performed using IMB SPSS Statistics v25.0.

Materials required

Assuming 40 patients in each arm, that will require 1 bottle of Larri® Oral spray or Placebo a month for two months, we anticipate the following costs:

|  |  |  |  |
| --- | --- | --- | --- |
| Material | Amount | Cost per unit | Total |
| Larri® Oral Spray | 80 bottles | $19.95 | $1,596 |
| Placebo | 80 bottles | $19.95 | $1,596 |
| Peptest Kit | 112 kits | $220 | $16,800 |
| Total |  |  | $19,992 |

Larri Oral Spray – 80 bottles (1 bottle a month, 40 patients, 2 months)

Placebo oral spray – 80 bottles

Peptest kits – 112 (anticipation of negative peptest excluding patients from trial)

The senior author has discussed the above costs with ENT Technologies (company which produces Larri® Oral Spray) and they have agreed to fund this project up to $20,000 AUD.

Once ethics approval has been granted, we aim to contact several local compounding pharmacies for their assistance in producing a suitable placebo product which will match Larri Oral Spray regarding a similar bottle and taste (mint flavour).

*Information about the drug being tested*

Approved name: Larri Oral spray

Trade Name: Larri Oral spray

Manufacturer: ENT Technologies Pty Ltd

Supplier: ENT Technologies Pty Ltd

Approved therapeutic indication: for gastro-oesophageal reflux disease and laryngopharyngeal reflux disease, available over-the-counter, 8 sprays a day, two sprays after breakfast, lunch, and dinner, and two sprays before bed.

Believed mode of action: Three active ingredients

* Magnesium alginate: creates a barrier to protect tissues from refluxate
* Sodium hyaluronate: likewise creates a barrier to protect tissues
* Camellia Sinensis: otherwise known as green tea extract, naturally soothes and relives the symptoms of inflammation.

No known/published adverse events or contra-indications

Anticipated outcomes, results, and future plans

We anticipate that the Larri® Oral Spray will be efficacious in treatment of LPR, and anticipate that this will be reflected in participants 8-week RSI questionnaire. We anticipate its treatment effect will be greater than that of placebo.

We aim to publish these results and present our findings in relevant medical journals and conferences.

Conflicts of interest

None to declare.

References

1. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice. 2002;16(2):274-7.

2. Bor S, Capanoglu D, Vardar R, Woodcock AD, Fisher J, Dettmar PW. Validation of Peptest in Patients with Gastro-Esophageal Reflux Disease and Laryngopharyngeal Reflux Undergoing Impedance Testing. J Gastrointestin Liver Dis. 2019;28(4):383-7.

3. Guo Z, Jiang J, Wu H, Zhu J, Zhang S, Zhang C. Salivary peptest for laryngopharyngeal reflux and gastroesophageal reflux disease: A systemic review and meta-analysis. Medicine (Baltimore). 2021;100(32):e26756.