

A Hospital Based Prospective Study to Evaluate the Role of Magnesium Supplement in Laryngopharyngeal Reflux Disease

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Conflict of interest: Nil

Abstract

Aim: To evaluate the association between Mg intake and the risk of reflux disease and that the addition of magnesium supplements should be considered and added to the LPRD treatment protocol for adults in accordance with the dietary reference intake (DRI).

Material & Methods: This is a hospital based prospective study done over a period of 1 year conducted in the Department of ENT, MP Birla Hospital & Priyamwada Birla Cancer Research Institute, Satna (MP), India, in patients presenting with symptoms suggestive of LPR, attending the ear, nose and throat (ENT) out-patients' department (OPD) of the age group 18-65 years.

Results: In both the groups the p value was calculated to be <0.05 and was found to be statistically significant. Both the groups showed appreciable improvement in their mean RSI and RFS score at 1 month and 3 months follow-up. In both the groups the p value was calculated to be <0.05 and was found to be statistically significant.

Conclusion: Addition of magnesium supplements along with the regular treatment for LPRD, can improve LPRD symptoms and should be considered in the treatment protocol of LPRD.

Keywords: Laryngopharyngeal reflux disease, Magnesium supplements, GERD, Reflux treatment

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Introduction

Laryngopharyngeal reflux (LPR) is an inflammatory condition of the upper aero digestive tract tissues caused by the direct and indirect effects of gastroduodenal content reflux, which may induce morphologic changes in the interested tract [1]. Common laryngeal findings are arytenoid and vocal cord erythema, posterior commissure hypertrophy, and arytenoid oedema [2-4]. Patients with LPR often experience hoarseness, globus sensation, throat clearing, cough, excess throat mucus, and postnasal drip [4]. LPR

is associated with a poor quality of life and a significant healthcare cost [1, 4].

Although the prevalence of LPR is still unclear due to a lack of a gold standard for its diagnosis, it was estimated that LPR represents up to 10% of otorhinolaryngologists' consultations [6, 7]. Additionally, an increase in the number of medical visits because of reflux, either LPR or gastro esophageal reflux disease (GERD), and in the number of anti-reflux prescriptions has been observed over the

last decades [8], suggesting that reflux is an increasingly spread health issue.

Typical symptoms of GERD are heartburn and regurgitation, rendering the distinction between GERD, FH, and RH complicated. To improve the diagnosis of GERD, the Gastro esophageal Reflux Disease Working Group of the International Working Group for Gastrointestinal Motility and Function created a consensus document to determine modern indications for esophageal testing in GERD and define criteria for the clinical diagnosis of GERD [9]. Diagnosis and investigation of GERD is commonly based on questionnaires, including the Gastrointestinal Symptom Rating Scale (GSRS) [10] and Frequency Scale for Symptoms of GERD (FSSG) [11].

Gastro esophageal reflux is not the only cause of LPR, but rather it is a multifactorial syndrome with a vast clinical representation and with complications, so it requires a multidisciplinary approach.

Magnesium is the most abundant intracellular divalent cation in the body. It plays an essential role in several physiological and biochemical processes. 50-60% of total magnesium is stored in the bones, about 40% is intracellular (mainly in muscles) and only 1% is found in extracellular fluid.[12]

Approximately one third of the average daily magnesium (Mg) intake (about 360 mg; 15 mmol) is absorbed in the small intestine through both a saturable transport system and passive diffusion, while another 20 mg (0.8 mmol) is absorbed in the large bowel. Conversely, almost 40 mg (1.7 mmol) of magnesium is excreted in intestinal Secretions. [13]

Mg helps relieve GERD and consequently LPRD by two mechanisms. Mg plays a major role in regulation of muscle contraction, and it helps smooth muscles to relax. It plays a role in the action of

pyloric sphincter. When the digestion of food in the stomach is complete, the pyloric sphincter relaxes, thereby allowing food to enter the small intestine for further digestive process. In case of magnesium deficiency, the pyloric sphincter fails to relax as often as it should, which impairs gastric emptying. When the food remains in the stomach for a longer time, it creates pressure on the LES, causing it to open upwards and thereby causing acid reflux.

Another mechanism by which Mg helps relieve GERD is by its neutralizing action on the gastric acid. Therefore, it may be pertinent to achieve optimal Mg intakes in patients with LPRD.

The primary aim of this study was to evaluate the association between Mg intake and the risk of reflux disease and that the addition of magnesium supplements should be considered and added to the LPRD treatment protocol for adults in accordance with the dietary reference intake (DRI).

Material & Methods:

This is a hospital based prospective study done over a period of 1 year conducted in the Department of ENT, MP Birla Hospital & Priyamwada Birla Cancer Research Institute, Satna (MP), India, in patients presenting with symptoms suggestive of LPR, attending the ear, nose and throat (ENT) out-patients' department (OPD), of the age group 18-65 years.

Methodology

The data was collected prospectively by questionnaire and clinical examination. All the patients presenting with symptoms like feeling of lump on the throat, changes in voice, difficulty in swallowing, chronic cough, excess throat mucus, heartburn and breathing difficulty were first clinically examined including examination with 70-degree Karl Storz endoscope.

Exclusion criteria were habit of smoking or tobacco chewing, recent history of

upper respiratory tract infection, history of any systemic inflammatory disease, voice abuse, thyroid mass, laryngeal tumors and vocal nodules and polyps and RFS below 7.

A total of 260 patients were included in the study. After obtaining informed verbal consent, they were interviewed with

predetermined questionnaire of reflux symptom index (RSI) (Table 1). Then video laryngoscopy was done in each of the patients and reflux finding score (RFS) (Table 2) was obtained. A RFS score above 7 and RSI above 13 were considered suggestive of LPRD.

Table 1: Complaint.

| Complaint | Score |
|--|-------------|
| Sensations/something sticking in your throat | 0 1 2 3 4 5 |
| Throat clearing | 0 1 2 3 4 5 |
| Excess throat mucous/postnasal drip | 0 1 2 3 4 5 |
| Difficulty swallowing food, liquids or pills | 0 1 2 3 4 5 |
| Hoarseness/change in voice | 0 1 2 3 4 5 |
| Coughing after you ate or after lying down | 0 1 2 3 4 5 |
| Breathing difficulties/choking | 0 1 2 3 4 5 |
| Chronic cough | 0 1 2 3 4 5 |
| Heart burn, chest pain, indigestion, or stomach acid coming up | 0 1 2 3 4 5 |
| Total | |

Table 2: Finding.

| Finding | Score |
|----------------------------------|---|
| Erythema/hyperemia | 2=arytenoids only; 4=diffuse |
| Diffuse laryngeal edema | 1=mild; 2=moderate; 3=severe; 4=obstructing |
| Subglottic edema | 2=present; 0=absent |
| Vocal fold edema | 1=mild; 2=moderate; 3=severe; 4=polypoid |
| Ventricular obliteration | 2=partial; 4=complete |
| Posterior commissure hypertrophy | 1=mild; 2=moderate; 3=severe; 4=obstructing |
| Granuloma/granulation | 2=present; 0=absent |
| Thick endolaryngeal mucus | 2=present; 0=absent |

Questionnaire for RSI (Reflux Symptoms Index):

It included name, date and the question: within the last month, how did the following problems affect you? (0-5 rating scale with 0=no problem and 5=severe). Normative data suggests that a RSI of greater than or equal to 13 is clinically significant. Therefore a RSI>13 may be indicative of significant reflux. Prior

informed consent was signed by all the participants enrolled as per guidelines and standards of research using human beings. The study was given approval by the institutional ethics committee of the hospital.

Data was analyzed for age and sex distribution. Both male and female were divided in 3 age groups - less than 30 years, 30 to 50 years and above 50 years.

In each group, mean RSI and RFS (Reflux Finding Score) were correlated between same age groups. The presenting symptoms and signs were analyzed for their relative percentage. The study population was then divided into 3 groups based on RSI score (group A: score below 13, group B: score 13-20, group C: score above 20). In each group, the mean value of different signs was calculated and analyzed for their correlation with disease severity.

Finally, the study population was divided into 3 groups based on RFS score (8 to 10, 11 to 14 and above 14). In each group, patients were randomly assigned to two groups- one to be treated with esmaprazole 40 mg capsules and alginate syrup and the other with esmaprazole 40 mg capsules, alginate syrups and magnesium glycinate 250 mg supplement. All patients were thoroughly counselled for lifestyle modifications.

The patients were followed up at 1 month and 3 months from initiation of medication and review scoring of RSI and RFS were done. Data was analyzed to ascertain the role of magnesium glycinate. The patients, who were under adequate treatment and following lifestyle modifications properly for at least 2 months but showing no improvement, were advised to follow a specially formulated reflux induction diet habit for 2 weeks and followed up to find out its impact.

The data was analyzed descriptively with Microsoft excel and statistical package for the social sciences (SPSS) version 21 using appropriate tests

Results:

Table 3: Out of total 260 cases, 139 (60.5%) were females and 121 (39.5%) were males. So female: male ratio was 1.14 :1.

Table 4: Out of 139 female patients, 23.71% (n=23) were below 30 years,

64.95% (n=63) were within 30 to 50 years and 11.34% (n=11) were above 50 years. Out of 121 male patients, 19.02% (n=31) were below 30 years, 63.19% (n=103) were within 30 to 50 years and 17.79% (n=29) were above 50 years.

Table 5: Both the groups showed appreciable improvement in their mean RSI and RFS score at 1 month and 3 months follow-up. In both the groups the p value was calculated to be <0.05 and was found to be statistically significant.

Figure 1: Foreign body/sticky sensation in throat was the foremost presenting complaint found in 70.3% of the study population, followed by excessive throat mucus (65.2%) and constant throat clearing (48.1%). Hoarseness of voice was seen in 8.1% of the patients. Dysphagia and dyspnea were the least common symptoms noticed, 16% and 3% respectively. A significant number of patients had overlap of two or more symptoms. Both the groups showed appreciable improvement in their mean RSI and RFS score at 1 month and 3 months follow-up. In both the groups the p value was calculated to be <0.05 and was found to be statistically significant.

Figure 2: Among the laryngeal signs of LPRD, granular pharynx, laryngeal erythema and posterior commissure hypertrophy were present in all the cases. 73% of the cases had diffuse laryngeal oedema and thick endolaryngeal mucus ('positive string sign') was noted in 36.4% cases. Subglottic edema and ventricular obliteration were rare findings, found only in 11% and 8% cases respectively.

The study patients were randomly divided into two groups one treated with esmaprazole 40 mg capsules and alginate syrup and the other with esmaprazole capsules, alginate syrup and magnesium glycinate (250 mg) supplement.

Both the groups showed appreciable improvement in their mean RSI and RFS

score at 1 month and 3 months follow-up. In both the groups the p value was

calculated to be <0.05 and was found to be statistically significant.

Table 3: Prevalence of LPRD by sex

| Sex | Prevalence | % |
|---------|------------|-------|
| Females | 139 (60.5) | 62.69 |
| Males | 121(39.5) | 37.31 |

Table 4: Prevalence of LPRD by age groups in both sexes

| Sex | Age group (years) | Prevalence | % |
|---------|-------------------|------------|-------|
| Females | <30 | 23 | 23.71 |
| | 30-50 | 63 | 64.95 |
| | >50 | 11 | 11.34 |
| | Total | 97 | 100 |
| Males | <30 | 31 | 19.02 |
| | 30-50 | 103 | 63.19 |
| | >50 | 29 | 17.79 |
| | Total | 163 | 100 |

Table 5: Mean RSI and RFS over both sexes in different age groups

| Sex | Age group (years) | Mean RSI | Mean RFS |
|---------|-------------------|----------|----------|
| Females | <30 | 17.8 | 13.3 |
| | 30-50 | 18.7 | 14.4 |
| | >50 | 16.3 | 12.6 |
| Males | <30 | 12.8 | 10.2 |
| | 30-50 | 14.2 | 12.7 |
| | >50 | 13.1 | 11.0 |

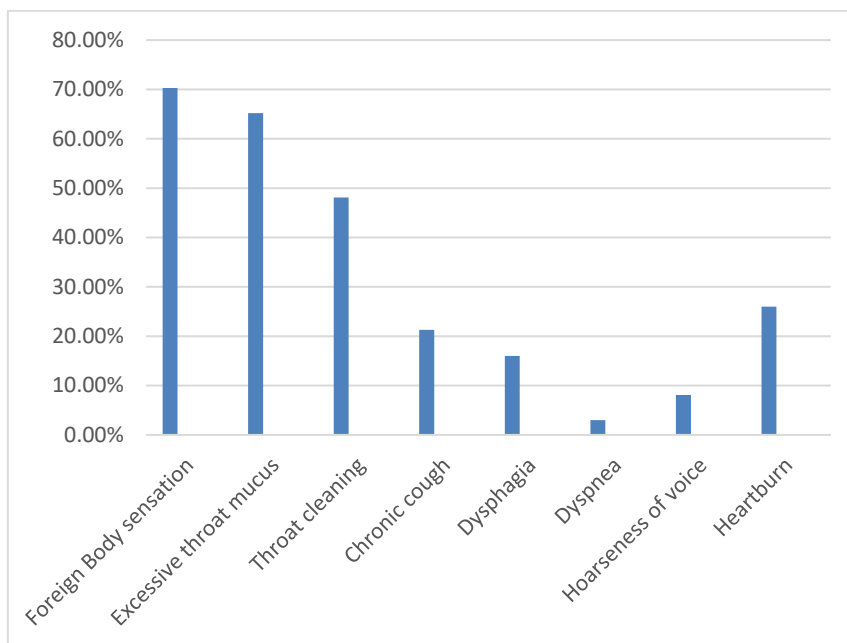


Figure 1: Symptoms among patients with LPRD.

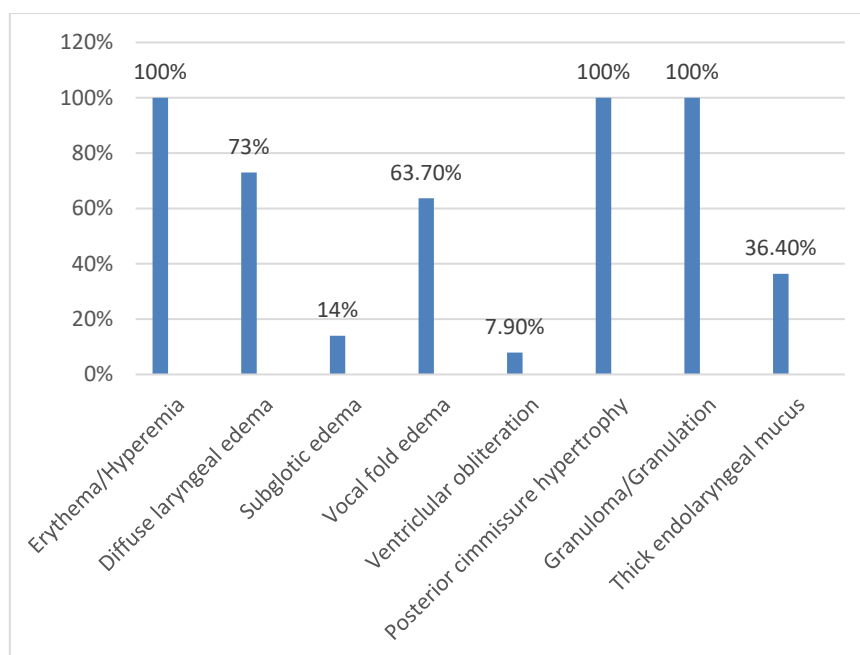


Figure 2: Endoscopic findings among patients with LPRD.

Discussion:

Probiotics of the genera *Lactobacillus* and *Bifidobacterium* are associated with modulations in the immune response and antagonistic activity toward potential pathogens through the production of short-chain fatty acids, such as lactic acid. Further, probiotics accelerate gastric emptying by interacting with stomach mucosal receptors, which are suspected of triggering transient lower esophageal sphincter relaxation, one of the pathophysiological mechanisms of GERD [14]. In addition, probiotics can be beneficial for small intestinal bacterial overgrowth, interfering with immunity or intestinal motility under various conditions [15].

McGlashan et al. conducted a RCT on 49 patients comparing the efficacy of a liquid alginate suspension (*Gaviscon® Advance*) to placebo in reducing LPR signs and symptoms [16]. They found a superiority of the alginate for LPR symptoms as measured by the RSI both at 2 and 6 months. A significant reduction of the RSI was reported also by Tseng et al. in a RCT

comparing alginates (*Alginos*) to placebo after 8-weeks of treatments in 80 patients with LPR, although it did not significantly differ to the RSI reduction of the placebo [17]. Another study compared the effect of the alginate (*Gaviscon® Advance*) alone to the efficacy of the alginate as an add-on treatment to PPIs in 72 patients with LPR [18].

A prospective multicenter study conducted in 2014 concluded that pantoprazole magnesium dehydrate 40 mg once daily for 4 weeks significantly improves GERD symptoms and that it is a safe, effective and well tolerated drug. The fact that pantoprazole magnesium has a prolonged elimination half-life compared with pantoprazole sodium is likely due to the slow dissolution of the magnesium-containing tablets in the stomach, resulting in reduced solubility which may result in longer gastric acid suppression for day-time and night-time symptom control.[19]

Another study says that one of the strategies to increase PPI efficacy is to use magnesium formulations such as in

esomeprazole, omeprazole or pantoprazole.[20]

Other studies using higher doses of PPIs failed to detect a significant improvement in videolaryngoscopic findings after the same treatment period. In the trial by Noordzij and colleagues assessing the efficacy of 40 mg omeprazole twice a day, none of the laryngeal signs of LPR significantly changed over the course of the study [21]. However, the baseline laryngoscopic assessment already showed mild objective laryngeal inflammation. The RCT by WO and colleagues analyzed the efficacy of a 12-week treatment with 40 mg pantoprazole and reported no change in the RFS score in the treatment groups, despite the patients reported a relief of LPR symptoms [22].

A study conducted in rats show that orally administered L arginine and L glycine are highly effective against acid reflux esophagitis.[23] However its role in humans has to be studied and the role of magnesium glycinate combination needs to be evaluated.

An Ireland population-based study indicated that high intake of Mg may protect against reflux esophagitis and Barrett's oesophagus. The protective effect of Mg may be particularly pronounced in the context of a low Ca: Mg ratio intake. [24,25]

Conclusion:

Addition of magnesium supplements along with the regular treatment for LPRD, can improve LPRD symptoms and should be considered in the treatment protocol of LPRD.

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