Efficacy of Super High Dose Proton Pump Inhibitor Administration in Refractory Laryngopharyngeal Reflux: A Pilot Study

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Summary: Objectives. Proton pump inhibitors (PPIs) are the mainstay of current medical management for laryngopharyngeal reflux (LPR) but may be insufficient in managing some patients' disease. This study was designed to investigate the effectiveness of superdose PPI therapy in the improvement of 24-hour pH impedance studies and stroboscopy findings in patients with LPR refractory to standard dosing (BID PPI).

Study Design. Retrospective chart review.

Methods. This study examined 35 patients ranging from 20 to 76 years diagnosed with refractory LPR who were treated with super high dose PPIs. Reflux finding scores (RFS) obtained by three blinded raters and 24-hour pH impedance study scores were compared for patients on standard and then super high dose PPI regimens.

Results. Statistical analysis of the stroboscopy evaluation revealed a modest but statistically significant decrease in the RFS scores for those patients on super high dose therapy, with good intrarater reliability. The DeMeester score showed no significant change between standard and super high dose regimens. The results of the 24-hour pH impedance monitoring showed no statistically significant decrease in acid reflux episodes despite an average of 7.6 fewer proximal acid reflux episodes.

Conclusion. Super high dose therapy seems to improve laryngeal signs of irritation as reflected by RFS. This improvement was not reflected in our patient population's severity of reflux while on super high dose therapy when compared with standard LPR therapy as measured by 24-hour pH impedance monitoring, although this finding may reflect selection bias. RFS and 24-hour pH impedance may be insufficiently sensitive to detect improvements in LPR with adequate treatment.

Key Words: Laryngopharyngeal reflux–LPR–Proton pump inhibitor–Super high dose proton pump inhibitor–Impedance testing–Reflux finding score.

INTRODUCTION

Laryngopharyngeal reflux (LPR) is the retrograde flow of gastric contents into the larynx and pharynx. Patients with LPR typically present with hoarseness, throat clearing, postnasal drip, dysphagia, cough and globus, and LPR has been implicated in other chronic illnesses such as asthma.[1] Although LPR is diagnosed in as many as 80% of patients with voice complaints, there is abundant controversy surrounding its diagnosis and treatment.[1,2]

LPR typically is treated medically with a combination of proton-pump inhibitors and/or histamine-2 antagonists with the intent of reducing the acid content of the refluxate. Proton pump inhibitors (PPIs) generally are prescribed once or twice daily for LPR. Some patients, despite our standard treatment twice daily, experience persistent symptoms. Unremitting laryngeal irritation typical of LPR may be noted on stroboscopy, and continued proximal acid exposure may be seen on 24-hour pH impedance monitoring of patients on antireflux medication. There has been no consensus on effective management for these patients, although many are referred for so-called "reflux surgery" such as Nissen fundoplication. This study introduced and investigated the efficacy of a super high dose PPI regimen for treating patients with refractory LPR.

METHODS

The study was performed following approval from the Drexel University College of Medicine Institutional Review Board (IRB Project #1044677, Protocol #19945).

Study objectives

1. Determine whether super high dose PPI therapy improves LPR in patients refractory to standard dosing as measured by impedance scores and reflux finding score (RFS).
2. Determine whether the DeMeester score is a useful measure of efficacy of treatment of refractory LPR.
3. Determine whether RFS correlates with severity of acid reflux (as measured by proximal acid reflux).

Study design and patient population

The study was a retrospective chart review with blinded reviews of previously recorded strobovideolaryngoscopic

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TABLE 1.
Patient Demographics

N	35
Age (y)	Range = 20–76 Median = 54 Standard deviation = 15
Sex	Men = 14 Women = 21

examinations. The study population consisted of patients from the senior author's (R.T.S.) tertiary laryngology practice with chief complaints of dysphonia and symptoms and signs consistent with LPR (Table 1). All subjects underwent dynamic voice assessment and strobovideolaryngoscopy with flexible and rigid endoscopes, using a protocol that has been published previously.[3] LPR was identified by suggestive laryngeal appearance on strobovideolaryngoscopy. Twice daily proton-pump inhibitors and nighttime histamine-2 antagonists were prescribed for all patients. Patients considered refractory to this "standard" treatment regimen had persistent symptoms, unremitting signs of laryngeal irritation typical of LPR on strobovideolaryngoscopy (such as those described within RFS[4]), and/or continued proximal acid exposure as evidenced by 24-hour pH impedance monitoring (described below). Reflux was considered refractory when patients failed to improve subjectively (eg, reduction in symptom frequency or severity) or based on stroboscopic findings following at least 3 months on standard therapy. Twenty-four–hour pH impedance studies were obtained on most patients to determine whether uncontrolled acid reflux was present; initially, some patients were placed on super high dose therapy empirically; however, now we obtain studies on all patients before super high dose therapy initiation. Refractory patients were started on super high dose therapy, defined as 1.5 or 2 times the usual BID dosing of proton-pump inhibitors, depending on the patients' symptoms, signs, and findings on continued pH impedance monitoring (Tables 2 and 3). Repeat 24-hour pH impedance studies were ordered for patients who did not appear to have LPR controlled well (clinically) on super high dose PPI therapy (14 of 35). In addition, six patients on whom we ordered pH impedance studies elected to undergo capsule testing on which information is available only about distal reflux; these data are also included in the analysis. Additionally, all patients on super high dose PPI also were maintained on nightly histamine-2 antagonists (ranitidine). Medication compliance was documented and confirmed in the patient records.

Study inclusion criteria were age >18 years, patients diagnosed with acid reflux episodes despite BID daily dosing of proton-pump inhibitors who subsequently took higher than BID daily dosing of PPIs, and medication compliance. Exclusion criteria included age <18 years, history of reflux surgery (eg, Nissen fundoplication), those taking alternative/breakthrough medication regimens (ie, over-the-counter antacids, motility agents, and so on), noncompliant patients, patients with known intralaryngeal pathology (eg, masses), and those whose laryngeal examinations were inadequate for evaluation.

Combined 24-hour pH impedance monitoring

Patients underwent pH impedance monitoring while on standard (BID) dosing as well as super high dose PPI therapy. Patients were referred to an esophageal laboratory for testing. At the laboratory, event diaries were given to patients to record pertinent events during the 24-hour monitoring period such as symptom occurrence, positional changes (recumbent or upright), and timing of meals. Information about medication regimen and timing, presenting symptoms, and demographics (age, gender, and so on) was recorded before monitoring.

Impedance monitoring was performed over approximately 24 hours using a combined impedance-pH monitoring device (Sandhill Scientific, Inc., Highlands Ranch, CO). The device consists of a catheter with two pH sensors (gastric and distal esophageal) and six paired impedance sensors. Before placement, each sensor was calibrated using manufacturer-recommended standardized buffer solutions (pH 4.0 and 7.0). The catheter was placed transnasally to reach predefined positions (3, 5, 7, 9, 15 and 17 cm) above the lower esophageal sphincter; positioning was confirmed by manometry. The sensors communicated with a wired data recorder (pH Impedance Monitoring; Sandhill Scientific, Inc.). Data sampling frequency for both impedance and pH sensors was 50 Hz. At the conclusion of the 20- to 24-hour monitoring period, the catheter was removed, and the data recorder information was downloaded and interpreted using *BioView Analysis software* (Sandhill Scientific, Inc.), and a report was generated.

Timing and positioning (upright or recumbent) of acid (pH < 4) and non-acid (pH > 4) reflux were identified and recorded after both autodetection (Autoscan; Sandhill scientific) and confirmation by laboratory personnel. Numbers of proximal, distal, and total reflux episodes were recorded into the password-encoded spreadsheet, along with information about medication regimen. Data were reviewed by the senior authors (R.T.S. and P.O.K.).

Data were transcribed into an impedance report, which along with the individual tracings, was transferred to patients' charts. Symptom index was recorded as the number of symptomatic events (eg, cough, throat clearing, mucous, and so on) associated with reflux episodes (acid or non-acid) out of the total number of symptomatic events during the 24-hour period. Composite score analysis (Johnson/DeMeester score) also was recorded.

Data collection

Following IRB approval, data were collected retrospectively. Patients' charts were examined and relevant data were entered into a password-protected Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA). Patient confidentiality was maintained using a random patient numbering system. A separate, password-encoded spreadsheet was maintained containing both patient names and their respective numbers and was used for data decoding.