

# Study of Laryngopharyngeal Reflux Using pH-Metering in Immediate Post-op of Laryngectomized Patients

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**Objective:** Little is known about incidence of laryngopharyngeal reflux (LPR) and gastroesophageal reflux (GER) in the early postoperative period of laryngectomy. To evaluate the effect and characteristics of the LPR and GER in laryngectomized patients, by means of double pH-metry during the 48 hours after surgery.

**Material and method:** In 50 patients, 48-hour double-probe pH monitoring was performed in postoperative period following laryngectomy, after a intraoperative placement. Descriptive analysis of 4 variables of pH to level of the sensor proximal, and definition of the presence of esofagic reflux and LPR.

**Results:** The incidence of LPR in the postoperative of laryngectomy ranges between 30% and 40%. A esofagic reflux has been observed in 40%.

**Conclusions:** A high incidence of LPR and GER in the postoperative immediate of laryngectomized patients was found.

**Key words:** Laryngo-pharyngeal reflux. Pharyngo-laryngeal reflux. Gastroesophageal reflux. Laryngeal neoplasia. Laryngectomy. pH-metry.

## Estudio del reflujo laringofaríngeo mediante pH-metría en el postoperatorio inmediato de los laringectomizados

**Objetivo:** Se desconoce la incidencia de reflujo laringofaríngeo (RLF) y de reflujo gastroesofágico (RGE) en el postoperatorio reciente de las laringectomías. Nos propusimos evaluar la incidencia y las características del RLF y el RGE en pacientes laringectomizados, mediante pH-metría de dos canales durante las 48 horas posteriores a la cirugía.

**Material y método:** Estudio prospectivo de 50 pacientes mediante la colocación intraoperatoria de una sonda de pH de dos canales, el análisis descriptivo de cuatro variables de pH a nivel del sensor proximal y definición del RGE y el RLF.

**Resultados:** La incidencia de RLF en el postoperatorio de los laringectomizados oscila entre el 30 y el 40% y la de RGE, en el 40%.

**Conclusiones:** El RLF y el RGE se detectan en un porcentaje elevado de pacientes en el postoperatorio inmediato de las laringectomías.

**Palabras clave:** Reflujo laringofaríngeo. Reflujo faringolaringeo. Reflujo gastroesofágico. Neoplasia de laringe. Laringectomía. pH-metría.

## INTRODUCTION

Already at the end of the sixties, the association between laryngo-pharyngeal reflux (LPR) and several laryngeal lesions was recognized.<sup>1-5</sup> The finding that patients with neoplastic lesions of the larynx and pharynx often present laryngo-pharyngeal reflux has been confirmed.<sup>5-9</sup> In recent years, LPR

is being assessed as an important aetiopathological factor in several conditions in the otorhinolaryngological area.<sup>10-13</sup> For instance, it might be an independent carcinogenic factor or it may be a carcinogen in association with tobacco and alcohol.<sup>14</sup>

There is no study to date that has been conducted during the immediate postoperative period following laryngectomy to assesses laryngo-pharyngeal reflux objectively and directly in the immediate postoperative period in patients who have undergone total laryngectomy, by means of a reliable test such as dual-channel pH-metry. Only 1 study, performed by Seikaly et al,<sup>3</sup> included empirical anti-reflux treatment for laryngectomized patients and a much lower percentage of fistulae was observed and, hence, the relation between LPR and fistula formation was assumed. In our study, we

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have undertaken a descriptive analysis of the presence or absence of episodes of reflux in the postoperative period following laryngectomy and their number.

The prevalence of this condition remains unknown. It varies from 4%, in the general population, to approximately 40%, in patients who report otorhinolaryngeal symptoms or findings that have been related with reflux.<sup>15,16</sup> The figure increases in patients who already have a diagnosis of gastroesophageal reflux disease, bringing it up to 60%.<sup>17,18</sup>

Our hypothesis is that laryngo-pharyngeal reflux is common during the immediate postoperative period following laryngectomy and we considered the aim of describing the incidence and characteristics of LPR in the immediate postoperative period in all patients who have undergone either total or partial laryngectomy (horizontal supraglottic or frontolateral laryngectomy).

## MATERIAL AND METHODS

Fifty-five patients with a diagnosis of squamous cell carcinoma of the larynx and who subsequently underwent surgical treatment over a 2-year period were included. The inclusion criterion considered was: patients scheduled for laryngectomy due to laryngeal neoplasm. The exclusion criteria were: patients who presented exteriorization of the carcinoma beyond the larynx involving soft tissues of the neck or skin, and those cases in which data collection issues had been detected (eg, they could not be calibrated and/or their records were of scant duration due to numerous artefacts).

Of the 55 patients included in this study, 5 were later excluded for the following reasons: 2 of them suffered serious postoperative complications; in the other 3 patients, the probe had been ripped out or detached from the nasal pyramid during the immediate postoperative period; hence, full reflux data could not be recorded. Therefore, there was a total of 50 cases available for the study (40 total laryngectomies and 10 partial laryngectomies): 8 underwent horizontal supraglottic laryngectomy (HSGL); in 2 of them, it was extended to other areas (base of the tongue and right arytenoids), and in the other 2 patients, the partial technique performed consisted of a frontolateral laryngectomy. The distribution of laryngectomized patients according to the TNM classification in cancer of the larynx (UICC, AJCC, 1997) is as follows: I (10%), II (16%), III (32%), and IV (42%).

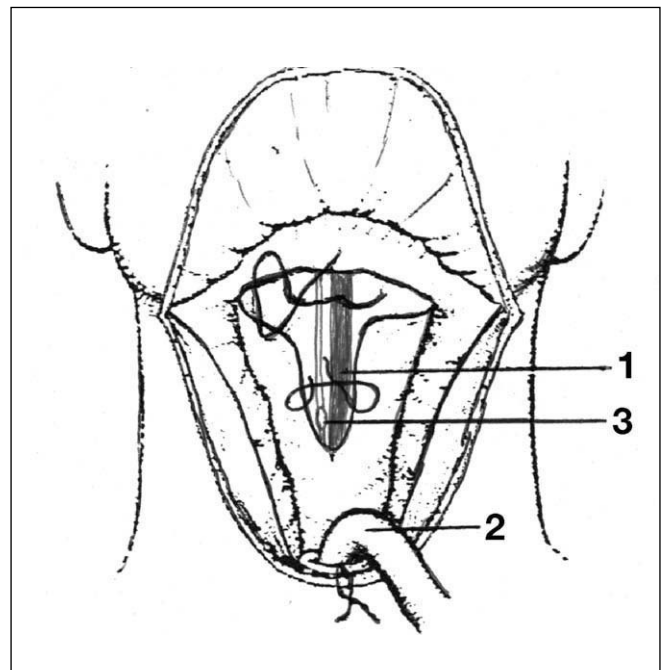
The Clinical Investigation Review Board approved the study in accordance with the Declaration of Helsinki and informed consent was obtained from each of the patients participating in the study.

All patients received prophylactic antibiotic therapy (clindamycin 600 mg and gentamycin 1.5 mg/kg of body weight, half an hour prior to surgery, and another 4 postoperative doses at 8-hour intervals) and patients were monitored to be sure that no anti-reflux treatment was initiated during the process of data collection; subjects requiring such treatment were excluded from the study.

For the purposes of recording pH and posterior analysis, pH-metry equipment (Liberty System, Synectics Medical®

medical-surgical equipment) was used consisting of the following components: portable Digitrapper Mark III® (MK III) brand pH-meter, which provides standard monitorization of 2 pH channels; monocrystalline pH catheter with a reference electrode and 2 sensors (proximal and distal) 15 cm apart; software to collect and analyze the recorded data (Esophogram®) and buffer solutions, pH 7.01, and 1.07, for the prior calibration of the pH probe.

The catheter was calibrated prior to placement in order to proceed to record the pH in each laryngectomized subject. Once the larynx has been excised during surgery and prior to pharyngeal closure, the catheter is inserted under direct vision through the same nostril in which the nasoesophageal Rush probe (100% silicon, T/Silmag; 0.6 mm diameter; 45 cm long) had been placed. We check that the distal electrode is located inside the oesophagus and that the proximal one is situated at the level of the lower end of the pharyngeal closure; it was placed in the lowermost area in the case of partial laryngectomies (Figure 1). Once the operation has concluded and the patient is in the recovery room, the portable pH-meter is connected and started. Once the data corresponding to the 48 postoperative hours have been completed, the pH probe is disconnected and withdrawn, and the data are transferred to the software programme where we can revise them and eliminate any artefacts that may have been produced during pH data collection, as well as the episodes of "pseudo reflux," by deleting falls in pH at the proximal sensor that had not been preceded by a fall in pH at the distal probe. Given the characteristics of the study population, most of the recordings were carried out in decubitus.



**Figure 1.** Placement of the proximal electrode of the pH probe just prior to the caudal area of the pharyngeal closure following total laryngectomy. 1: nasogastric probe; 2: tracheostomy cannula; 3: pH probe, with a view of the proximal electrode.

The pH parameters used to study reflux in each patient are obtained from deMeester's scale, present on the pH record. The quantitative pH variables that we analyzed at both the proximal and distal electrodes are as follows: percentage of time with pH less than 4.0, number of acid refluxes, total time of pH below 4.0, and area of reflux. An episode of acid reflux is described as when the pH falls below 4.0 for at least 5 seconds. The area of reflux is the product of multiplying the mean pH below 4.0 by the time during which the pH has remained below 4.0 (pH  $\times$  min). Likewise, the diagnosis of LPR has been established on the basis of 2 criteria, bearing in mind the values of the variable percentage of time with a pH value  $<4$ , described by 2 of the most relevant research teams working on the subject: on the one hand Koufman,<sup>7</sup> who considers that any percentage other than 0 would indicate that there has been acid reflux, and on the other hand, Bove et al,<sup>19</sup> whose criterion is stricter: they consider LPR on the basis of figures  $\geq 0.2\%$ .

In several studies<sup>20,21</sup> abnormal oesophageal probe recordings at the distal oesophageal probe are defined when the percentage of time with pH $<4$  in  $>8.1\%$  of the time the patient is standing or  $>2.9\%$  of the time he/she is lying down and/or  $>5.5\%$  of the total time. Therefore, we have considered that there is pathological distal reflux when the percentage of time with pH of less than 4 is greater than or equal to 5.5% for the purposes of our analysis.

The descriptive study has been performed and express the results of the continuous quantitative variables by means of central tendency statistics and percentile calculation. Frequency and absolute percentage tables were used for both qualitative and quantitative variables and 95% confidence intervals (CI) were calculated in order to estimate the various proportions.

## RESULTS

The ages ranged between 39 and 83 years, with a mean (standard deviation) of 61.68 (10) years. Of the 50 patients, 48 were males and 2 were female. Half of the patients (52.5%) acknowledged that they drank large amounts of alcohol, greater than 80 g of ethanol per day, and 7.5% claimed to be moderate drinkers (less than 80 g), 40% denied alcohol use. Insofar as smoking habits are concerned, 62.5% smoked more than 20 cigarettes per day; 20% were moderate smokers ( $<20$  cigarettes/day or former smokers), and the remaining 17.5% did not smoke. Seventy-four percent of the participants had advanced tumours (stages III, IV). As for the laryngectomy technique performed, 10 patients (20%) had undergone a partial technique and in 40 (80%), total laryngectomy had been performed.

With respect to the clinical symptoms of GER, such as regurgitation, pyrosis, retrosternal pain, dysphagia, coughing, or other symptoms, 4 patients reported at least 1 of these symptoms; however, although 3 of them had a history of ulcer, they were asymptomatic at the time. No proximal laryngo-pharyngeal reflux was detected in any of the participants who reported clinical evidence indicative of GER.

The percentage of time during which the pH was below 4 at the proximal electrode varied between 0 and 27.7%, with a mean of 1.73% (4.8). This low mean is due to the fact that there was a 0% percentage rate in 30 of the patients (60%) (Figure 2). Therefore, we can state that there was some degree of proximal reflux in 20 patients (40% of the sample). Of these 20 subjects, 7 (35%) presented very low proportions of time (0.1%-0.2%), and in 6 (30%), the percentage was greater than 5%, which represents acid reflux of at least 2.4 h (Figure 3). When we calculate percentiles, we see that 10% of the patients present a percentage of time with pH  $<4$  greater than 6.6% and 5% greater than 12% (Table). The data would be consistent with Koufman-Wiener's criterion, with a 95% CI of 26.42%-53.58%. According to Bove's criterion, proximal acid content was recorded in 15 (30%) (95% CI, 17.3%-42.7%).

The number of acid refluxes ranges from not a single episode up to 453 acid episodes at the level of the proximal electrode. The mean number of episodes is 26.9 (74.3). In 72%, at least 1 episode of reflux was detected; nonetheless, as also occurred with the percentage of time with pH  $<4$ , there were many patients in whom the number of refluxes was low; thus, 30% of the total patient sample had from 1 to 5 episodes recorded in their pH-metry. The median is 50 reflux episodes; 10% presented more than 61 reflux episodes, and 5%, more than 200 episodes.

The total time during which pH remained below 4 varied from 0 minutes detected up to 416 min (almost 7 h); the mean was 36.22 (89) min. In 23 patients (46%), not a single minute of proximal acid exposure was recorded and in 13 (26%), total reflux time was less than 5 min. In 11, the time during which subjects were exposed to an acid concentration of less than 4 was high or very high (between 15 and 416 min). The median was only 1 min. By calculating percentiles, we found that 10% presented a total time of exposure to pH  $<4$  of more than 2 h and 52 min and 5%, more than 4 h and 40 min.

The area of proximal reflux varied from 0 to 1117.5 pH units per minute. The mean was 69.7 (205.2). In 28%, the figures are high or very high (greater than 5); in 38%, it was less than 5 and in 34% of the patients, the area was 0. The median was 0.45; the 75th percentile was 18.35; the 90th percentile was 225.65, and the 95th percentile, 649.14.

The values corresponding to the variable "percentage of time with pH  $<4$  at the level of the distal sensor" in the study of the patients in whom total or partial laryngectomy had been performed varied from 0 to 63.5%. The mean was 8.5% (12.4)% and the median, 3.7%. Considering the criterion for defining the presence of distal reflux, pathological oesophageal reflux was found in 20 individuals, representing 40% of the total sample (Figure 4).

## DISCUSSION

Laryngopharyngeal reflux, also known as gastropharyngeal reflux (GPR), extraesophageal reflux, or acid pharyngeal reflux, is the passage of the gastric content beyond the

oesophagus, toward the laryngeal and/or pharyngeal area.

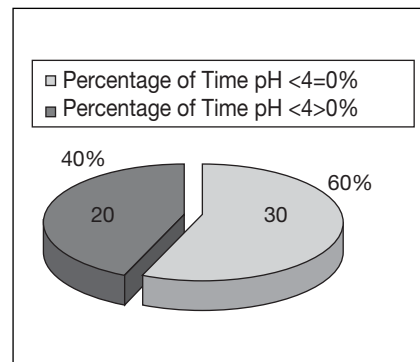
LPR differs from typical GER in some aspects, predominantly in its symptoms and lesions. It also varies with respect to the pH-metry pattern; LPR is more usual while standing. Treatment effectiveness in LPR calls for high doses of medication and protracted administration periods, in comparison with typical cases of GER. We must therefore consider laryngo-pharyngeal and gastroesophageal reflux as distinct processes.

Recent technological advances have made dual-channel pH-metry the most sensitive technique to determine whether there is acid reflux at the level of the proximal oesophagus and hypopharynx, thereby establishing the diagnosis of laryngo-pharyngeal reflux.<sup>7,22-26</sup> pH must be measured at a minimum of 2 places. The placement of a second sensor distal to the proximal probe is key to detecting episodes of "pseudo reflux." Once detected, we can proceed to eliminate them and thereby avoid errors in proximal pH measurements.<sup>27</sup>

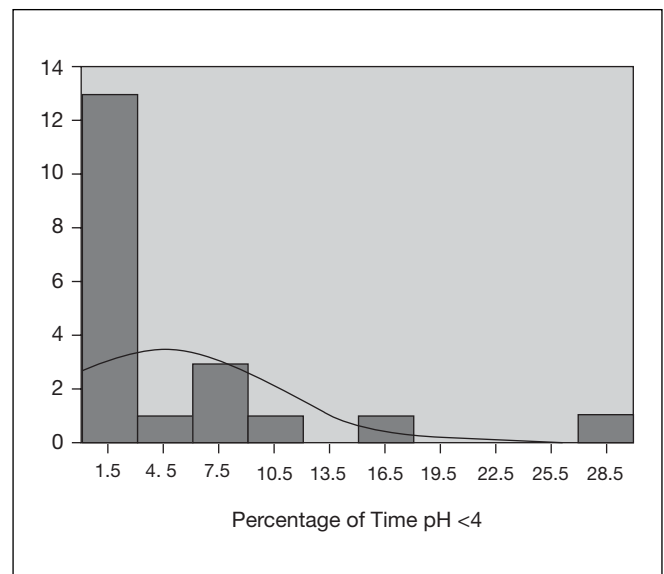
However, to date there is no international consensus with respect to monitoring laryngo-pharyngeal pH and we lack parameters that are universally accepted as normal. Several studies of the pH-metry of the proximal oesophagus carried out in healthy individuals have concluded that it is rare to detect acid exposure at this level<sup>26,28,29</sup> and therefore, a minimal presence of acid in the pharynx would be considered an abnormal event.<sup>7,25,30</sup> Nevertheless, other researchers disagree because they have found pharyngeal reflux in studies with healthy subjects.<sup>28,31,32</sup> Shaker et al<sup>33</sup> detected that only a single episode of acid reflux into the pharynx occurred while standing and not even 1 episode occurred while lying down in only 2 of the 12 healthy volunteers. According to Postma,<sup>32</sup> 1 or 2 episodes of pharyngeal reflux in a totally asymptomatic individual with normal findings in the laryngeal examination may be fairly unimportant unless that person is intubated, is to undergo laryngeal surgery or abuses his/her voice.

Another of the controversies that still remain with respect to double pH-metry is the placement of the proximal electrode. It varies from 1 author to the next: 20 cm above the lower oesophageal sphincter, just below the upper oesophageal sphincter or in the hypopharynx.<sup>7,22,32,34</sup> However, most coincide in that manometry continues to be the most widespread technique used to locate the upper oesophageal sphincter. We had no problem in locating it in our study, since the pH probe was placed during surgery under direct vision and we were able to place the proximal electrode at the height of the most caudal area of sutures in all cases.

As a novel feature, this research has evaluated the incidence and the characteristics of laryngo-pharyngeal and oesophageal reflux in the immediate postoperative period in patients on whom laryngectomy had been performed, by means of dual-channel pH-metry, over a 48-hour period. Given that to date, no other study of pH during the postoperative period following laryngectomies has been conducted, a comparative studies of our results is impossible. Nevertheless, we have assumed 2 criteria for defining LPR at the level of the proximal sensor in order



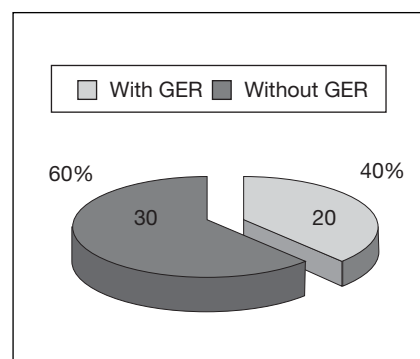
**Figure 2.** Diagram of sectors of patients in whom laryngectomy had been performed according to the variable percentage of time with pH less than 4 at the proximal electrode (n=50).



**Figure 3.** Values of the 20 laryngectomized patients who presented a percentage of time of pH <4 greater than 0 (n=20).

Percentiles 50, 75, 90, and 95 of the Percentage of Time With pH <4 in Laryngectomized Patients (n=50)

Percentiles	Values
P <sub>50</sub>	0%
P <sub>75</sub>	0.35%
P <sub>90</sub>	6.68%
P <sub>95</sub>	12.02%



**Figure 4.** Distribution of frequencies of laryngectomized individuals according to gastroesophageal reflux (GER) at the distal electrode (n=50).

to obtain a more comparative results of the incidence of laryngo-pharyngeal reflux in laryngectomized subjects. In our research, we have presented the results of the 4 pH values most widely studied in the literature in depth. Most authors agree in emphasizing the percentage of time with pH <4 as the most accurate diagnostic pH variable for laryngo-pharyngeal reflux.

The application of the 2 criteria for proximal reflux, according to the results of the percentage of time with pH <4 variable, enables us to state that of a significant number of patients who undergo either total or partial laryngectomy, in approximately one third (30%-40%), pharyngo-laryngeal reflux has been detected at the level of surgical closure during the 48 hours immediately following surgery. This figure is not negligible, although it is clear that in most cases the values of the percentage of time with pH <4 variable are small, even when a few present very high reflux values (8% of the total presented a percentage of time with pH <4 greater than 8.9, which represents more than 2 h).

No normal values have been established either for the number of acid refluxes, total time with pH <4 and area of reflux variables at the laryngo-pharyngeal level nor has there been any publication of results obtained in otorhinolaryngeal diseases, including laryngeal neoplasm. Overall in our research, the results for these three pH variables reveal a distribution of values that is similar to the one obtained with the percentage of time with pH <4, although a certain disagreement is seen due to the fact that the variables assume non-equivalent parameters.

The total time with pH <4 variable reflects in minutes the time during which the proximal sensor has picked up acid reflux. We must remember a 48-hour recording was carried out in our patients and this must be taken into account if comparative studies are to be set up in the future.

The results from Koufman's study<sup>7</sup> provides us with a 58% LPR rate in patients with neoplasm. This figure is greater than the one we found in our work, although Koufman's study includes a small sample (26 patients) and the conditions are also very different in the 2 studies. The study by Copper et al<sup>22</sup> corroborated Koufman's findings. In his analysis of 24 patients with neoplasm of the head and neck, he found a 62% incidence of LPR using a 24-hour outpatient pH-metry recording. Lewin et al,<sup>35</sup> with a larger sample size, studied 40 patients with early laryngeal carcinoma (T<sub>1</sub> or T<sub>2</sub>) or with dysplasia. The 24-hour pH-metry demonstrated that 85% of the patients had laryngo-pharyngeal reflux. Nevertheless, the incidence was modified greatly by the patient's position, which was standing in 91% versus supine in 9%. Therefore, these very dissimilar results might account for the lower percentage found in our study, due to the fact that our patients remained either supine or half sitting for the first 48 hours post-op; some of them began to walk around on the second day. Other special postoperative conditions worthy of note: lack of toxic substances, presence of probe, etc.

Galli et al<sup>36</sup> obtained similar results in a study conducted in 21 patients with squamous cell carcinoma of the larynx or hypopharynx and revealed pathological reflux in 80.9%.

The only study carried out in total laryngectomized patients was the one performed by Smit et al<sup>37</sup> that included 11 patients; the authors used pH-metry, with placement of the proximal electrode at the level of the upper oesophageal sphincter under direct vision by means of a flexible fibroscope. They determined a high incidence of gastropharyngeal (9/11) and gastroesophageal (7/11) reflux. However, in this study, the mean time elapsed since surgery was 1.4 years.

After the bibliographic review, we find that our incidence rates are somewhat lower than the ones reported by authors who have studied reflux in patients with laryngeal neoplasm, which varies between 58% and 85%. This discrepancy may be due to several reasons: on the one hand, in our patients, although most of them had a history of significant toxic habits, as expected, at the time they were informed of their diagnosis and/or treatment they quit their toxic habits and, of course, said habits are absent during the postoperative period and during pH recording. Moreover, our recording, because it was conducted over the 48 hours following surgery, entails that for the first 24 hours, laryngectomized patients have nothing *per os*; hydration and the electrolyte balance is maintained by intravenous drip, and it is only after 24 hours when strictly controlled feeding of specifically prepared food is begun via nasogastric tube. We cannot forget the fact that during the initial convalescence the individuals are lying down or semi-sitting. This would account for fewer episodes of reflux, since, as already commented, the typical pH-metry pattern associated with LPR is more common while standing.

In the light of the results obtained in this study, based on the fact that the incidence of acid reflux is considerable among laryngectomized patients, it seems logical to propose that an efficacious antireflux treatment be routinely administered during the postoperative period of all people undergoing laryngectomy. In connection with this, the study performed by Sarria et al<sup>38</sup> evaluated the effect of associating an antireflux agent, such as metoclopramide hydrochloride (Primperan®), into their standard protocol, which only included ranitidine, following total laryngectomy. Metoclopramide hydrochloride increases upper oesophageal sphincter tone, while facilitating gastric emptying and improves absorption of other drugs. Nausea is thereby decreased; it also has an anti-emetic effect due to its inhibitory action on the D<sub>2</sub> dopaminergic receptors. There was a 32.1% incidence of fistulae in the subset of total laryngectomized subjects (56 patients); however, it was different in the 2 groups: 39.4% in those who had only been treated with ranitidine and 21.7% in those who had received ranitidine plus metoclopramide. Nevertheless, in the statistical analysis, the  $\chi^2$  test did not reflect a probability of less than 0.05 ( $P=.198$ ); consequently, in this study statistically significant differences could not be established.

In conclusion, we would like to emphasize that LPR in the immediate postoperative period following laryngectomy is found in a high percentage of patients (95% CI, 26.42%-53.58%; mean, 1.73% [4.8]).

## REFERENCES

- Carrau RL, Khidr A, Crawley JA, Hillson EM, Davis JK, Pashos CL. The impact of laryngopharyngeal reflux on patient-reported quality of life. *Laryngoscope*. 2004;114:670-4.
- Ahmad I, Batch AJ. Acid reflux management: ENT perspective. *J Laryngol Otol*. 2004;118:25-30.
- Seikaly H, Park P. Gastroesophageal reflux prophylaxis decreases the incidence of pharyngocutaneous fistula after total laryngectomy. *Laryngoscope*. 1995;105:1220-2.
- Weber RK, Jaspersen D, Keerl R, Eikermann M, Mosges R. Gastroesophageal reflux disease and chronic sinusitis. *Laryngorhinootologie*. 2004;83:189-95.
- Kothe C, Schade G, Fleischer S, Hess M. Vocal cord dysfunction. An important differential diagnosis to bronchial asthma. *HNO*. 2004;52:261-4.
- Price JC, Jansen CJ, Johns ME. Esophageal reflux and secondary malignant neoplasia at laryngoesophagectomy. *Arch Otolaryngol Head Neck Surg*. 1990;116:163-4.
- Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope*. 1991;101 Suppl 1:1-78.
- Ward PH, Hanson DG. Reflux as an etiological factor of carcinoma of the laryngopharynx. *Laryngoscope*. 1988;98:1195-9.
- Freije JE, Beatty TW, Campbell BH, et al. Carcinoma of the larynx in patients with gastroesophageal reflux. *Am J Otolaryngol*. 1996;17:386-90.
- Wong RK, Hanson DG, Waring PJ, Shaw G. ENT manifestations of gastroesophageal reflux. *Am J Gastroenterol*. 2000;95 Suppl 8:S15-22.
- Toohill RJ, Kuhn JC. Role of refluxed acid in pathogenesis of laryngeal disorders. *Am J Med*. 1997;103:100S-6.
- Ulualp SO, Toohill RJ, Shaker R. Pharyngeal acid reflux in patients with single and multiple otolaryngologic disorders. *Otolaryngol Head Neck Surg*. 1999;121:725-30.
- Deschner WK, Benjamin SB. Extraesophageal manifestations of gastroesophageal reflux disease. *Am J Gastroenterol*. 1989;84:1-5.
- Galli J, Cammarota G, Calo L, Agostino S, D'ugo D, Cianci R, et al. The role of acid and alkaline reflux in laryngeal squamous cell carcinoma. *Laryngoscope*. 2002;112:1861-5.
- Koufman JA. Laryngopharyngeal reflux 2002: a new paradigm of airway disease. *ENT J*. 2002;81 Suppl 2:2-6.
- Eubanks TR, Omelanczuk PE, Maronian N, Hillel A, Pope CE, Pellegrini CA. Pharyngeal pH monitoring in 222 patients with suspected laryngeal reflux. *J Gastrointest Surg*. 2001;5:183-90.
- García-Compeán D, González MV, Galindo G, Mar DA, Treviño JL, Martínez R, et al. Prevalence of gastroesophageal reflux disease in patients with extraesophageal symptoms referred from otolaryngology, allergy, and cardiology practices: a prospective study. *Dig Dis*. 2000;18:178-82.
- Jaspersen D, Kulig M, Labenz J, et al. Prevalence of extra-oesophageal manifestations in gastro-oesophageal reflux disease: an analysis based on the proGERD study. *Aliment Pharmacol Ther*. 2003;17:1515-20.
- Bove M, Ruth M, Cange L, et al. 24-h pharyngeal pH monitoring in healthy volunteers: a normative study. *Scand J Gastroenterol*. 2000;35:234-41.
- Richter JE, DeMeester TR, Wu WC, et al. Normal 24-hour esophageal pH values: influence of age and gender. *Gastroenterology*. 1990;98:A122.
- Kahrilas PJ, Quigley EMM. Clinical esophageal pH recording: a technical review for practice guideline development. *Gastroenterology*. 1996;110:1982-96.
- Copper MP, Smit CF, Stanojcic LD, Devriese PP, Schouwenburg PF, Mathus-Vliegen LM. High incidence of laryngopharyngeal reflux in patients with head and neck cancer. *Laryngoscope*. 2000;110:1007-11.
- Conley SF, Warlin SL, Beste DJ. Proximal pH-metry for diagnosis of upper airway complications of gastroesophageal reflux. *J Otolaryngol*. 1995;8:295-8.
- Wiener GJ, Cooper JB, Wu WC. Reflux laryngitis and its sequelae. The diagnostic role of ambulatory 24-hour pH monitoring. *J Voice*. 1988;2:78-9.
- Wiener GJ, Morgan TM, Copper JB, et al. Ambulatory 24-hour esophageal pH monitoring. Reproducibility and variability of pH parameters. *Dig Dis Sci*. 1988;33:1127-33.
- Dobhan R, Castell DO. Normal and abnormal proximal esophageal acid exposure: results of dual-probe pH monitoring. *Am J Gastroenterol*. 1993;88:25-9.
- Jecker P, Schuon R, Mann WJ. The need for 24-h double probe pH monitoring in the diagnosis of laryngo-pharyngeal reflux. *HNO*. 2003;51:704-9.
- Yates PD, Pryde A, Maher L, Heading RC, Wilson JA. Pattern of ambulatory pharyngo-esophageal motility and pH-metry in healthy volunteers. *Clin Otolaryngol*. 2001;26:113-6.
- Jacob P, Kahrilas PJ, Herzon G. Proximal esophageal pH-metry in patients with "reflux laryngitis." *Gastroenterology*. 1991;100:305-10.
- Wiener GJ, Koufman JA, Wu WC, Cooper JB, Richter JE, Castell DO. Chronic hoarseness secondary to gastroesophageal reflux disease: documentation with 24-hour ambulatory pH monitoring. *Am J Gastroenterol*. 1989;84:1503-8.
- Ulualp SO, Toohill RJ. Laryngopharyngeal reflux. state of the art diagnosis and treatment. *Otolaryngol Clin North Am*. 2000;33:785-802.
- Postma GN. Ambulatory pH monitoring methodology. *Ann Otol Rhinol Laryngol Suppl*. 2000;184:10-4.
- Shaker R, Milbrath M, Ren J, et al. Gastroesopharyngeal distribution of refluxed gastric acid in patients with reflux laryngitis. *Gastroenterology*. 1995;109:1575-82.
- Richter JE. Ambulatory esophageal pH monitoring. *Am J Med*. 1997;103:S130-4.
- Lewin JS, Gillenwater AM, Garrett JD, Bishop-Leone JK, Nguyen DD, Callender DL, et al. Characterization of laryngopharyngeal reflux in patients with premalignant or early carcinomas of the larynx. *Cancer*. 2003;97:1010-4.
- Galli J, Cammarota G, Calo L, Agostino S, D'ugo D, Cianci R, et al. The role of acid and alkaline reflux in laryngeal squamous cell carcinoma. *Laryngoscope*. 2002;112:1861-5.
- Smit CF, Tan J, Mathus-Vliegen LMH, et al. High incidence of gastropharyngeal and gastroesophageal reflux after total laryngectomy. *Head Neck*. 1998;20:619-22.
- Sarria P, Tomas M, Mas S, Soler R, Romaguera A. Pharmacological prophylaxis of gastroesophageal reflux. Incidence of pharyngocutaneous fistula after total laryngectomy. *Acta Otorrinolaringol Esp*. 2000;51:239-42.