Effect of Perioperative Hypothyroidism on Pharyngocutaneous Fistula Formation Following Total Laryngectomy

Baran D Sumer¹, Deborah Larrison¹, Brett A Miles², John M Truelson¹, Chul Ahn³ and Larry L Myers¹*

¹Department of Otolaryngology - Head and Neck Surgery, University of Texas Southwestern Medical Center at Dallas, Dallas, TX
²Department of Otolaryngology – Head and Neck Surgery, Mount Sinai School of Medicine, New York, NY
³Department of Clinical Sciences, University of Texas Southwestern Medical Center at Dallas, Dallas, TX

Abstract

Objective: To compare the effects of perioperative hypothyroidism on postoperative pharyngocutaneous fistula (PCF) formation in patients undergoing total laryngectomy.

Study Design: Case series with chart review.

Setting: University-based, tertiary care hospitals.

Patients and Methods: We retrospectively analyzed 49 consecutive patients undergoing total laryngectomy between January 2003 and December 2007 having perioperative thyroid stimulating hormone (TSH) levels. We defined hypothyroidism according to American College of Clinical Endocrinology guidelines as serum TSH level above 4.5 mIU/mL. Patients were divided into 2 groups: Group I, comprised of hypothyroid patients and Group II, comprised of euthyroid patients. We collected demographic, clinical, laboratory and perioperative data for analysis.

Results: Group I had 10 patients (20%). Group II was matched in nearly all clinical and perioperative variables. Overall, 18 patients (37%) had postoperative PCF. Only 4 of these patients (40%) were from Group I compared to 14 patients (36%) from Group II (p=1.000). Thirteen patients (27%) underwent a concurrent thyroidectomy; 2 from Group I and 11 from Group II. PCF formation was not related to concurrent thyroidectomy (p=0.508). None of the other clinical variables studied (TNM stage, alcohol and tobacco use, preoperative albumin and hemoglobin level, prior radiotherapy, diabetes, neogullet closure type) were associated with PCF formation.

Conclusions: PCF formation is multifactorial and our data suggest that PCF is not singularly associated with perioperative hypothyroidism as defined by current standards. A greater degree of hypothyroidism may be required to affect PCF formation. Total laryngectomy should not be delayed secondary to moderately elevated pre-operative TSH values.

Keywords: Surgical complications; Pharyngocutaneous fistula; Laryngectomy; Wound infection; Head and neck cancer; Hypothyroidism

Introduction

One of the most challenging problems facing head and neck surgeons is wound healing. Wound complications after head and neck surgery are associated with increased patient morbidity, hospitalization, resource utilization, delays in starting adjuvant therapy and even mortality. After a total laryngectomy, perhaps the most devastating wound healing complication is the development of a pharyngocutaneous fistula (PCF).

The etiology of PCF formation following major head and neck surgery is multifactorial and the incidence varies greatly from 3% [1] to 65% [2]. Previous studies [3-10] have investigated predisposing factors of fistulization. The most frequently studied potential predisposing factors for development of PCF include various co-morbidities, low hemoglobin levels, poor nutritional status, previous radiation, previous tracheotomy, tumor site and stage, as well as the extent and technique of surgery [11]. Hypothyroidism is also frequently suggested to be a risk factor for postoperative wound complications. However, there are few data to support whether this metabolic derangement predisposes patients to the development of PCF after total laryngectomy.

Hypothyroidism is a frequent complication in patients treated for head and neck cancer, with reported incidences as high as 52% with multimodal therapy [12]. Its effect on PCF formation is controversial. Some investigators [13-15] report an association of hypothyroidism with PCF, while others [16] reported no clear association.

The purpose of this study was to determine the effects of perioperative hypothyroidism on the development of PCF in patients undergoing total laryngectomies.

Patients and Methods

We obtained approval to conduct this study from the Institutional Review Board of the University of Texas Southwestern Medical Center. We performed a retrospective chart review of the medical records of all patients that underwent a total laryngectomy over a five-year period from 2002 to 2007. We defined hypothyroidism according to American College of Clinical Endocrinology guidelines as a serum thyroid stimulating hormone (TSH) level above 4.5 mIU/mL. Patients were divided into 2 groups: Group I, comprised of hypothyroid patients; and Group II, comprised of euthyroid patients. We collected demographic

*Corresponding author: Larry L Myers, Department of Otolaryngology - Head and Neck Surgery, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9035, Tel. 214 648-5643; Fax: 214 648-9122; E-mail: larry.myers@utsouthwestern.edu

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(age, gender, ethnicity), social habits (tobacco, alcohol, illicit drug use), pre-operative (comorbidities, TNM stage, prior chemotherapy and/or irradiation) and perioperative laboratory (serum albumin, hemoglobin, TSH) and intraoperative (concurrent thyroidecstomy, type of neogullet closure) data for analysis. We defined a positive smoking history as greater than or equal to 20 pack-years. We arbitrarily defined an active smoking history as tobacco use within 5 years of diagnosis. We defined alcohol use as an average of 2 or more drinks daily.

Clinical and perioperative characteristics were compared between Group I and Group II using Fisher’s exact tests or chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. All statistical analyses were conducted with SAS 9.2 (SAS Institute Inc., Cary, NC). Statistical significance was assumed when p ≤ 0.05.

Results

Forty-nine patients with a mean age of 60.4 years (± standard deviation 10.7 years, range: 34.5 – 92.0 years) were analyzed. Most patients (94%) were male. The mean follow up was 18.2 months (± 15.3 months). Group I (hypothyroid) was comprised of 10 patients (20%) with a mean age of 62.9 years (± 7.7 years). Group II (euthyroid) was comprised of 39 patients (80%) with mean age of 59.7 (± 11.4 years).

Both Groups were matched in nearly all clinical and perioperative variables except for a higher number of patients in Group I receiving pre-operative irradiation (p=0.021) (Table 1).

Stepwise logistic regression analysis shows that pre-operative XRT and albumin were significant independent risk factors for hypothyroidism, not PCF formation, in this study. Patients with pre-operative XRT had 13.5 times higher chance of being hypothyroid than those without pre-operative XRT, after controlling the effects of albumin (95% CI [1.63, 111.97]). There was 83% less chance of having hypothyroidism for 1 mg/L increment of serum albumin after controlling the effect of albumin (95% CI [0.038, 0.773]).

Overall, 18 patients (37%) had postoperative PCF (Table 2). Of these, 4 patients were from Group I (40%) compared to 14 patients from Group II (36%), p = 1.000. Of the 31 patients without PCF, 6 patients (19%) were hypothyroid. This was not statistically different from the 4 of 18 patients (22%) with PCF, p=1.000. Eleven of the 18 patients with PCF (61%) underwent revision surgery to close the PCF. Only 1 patient of 31 patients without PCF (3%) underwent a revision surgery related to free flap (p < 0.0001).

The average TSH value for patients with PCF and without PCF was 2.64 mIU/mL ± 2.0 and 2.80 mIU/mL ± 4.56, respectively (p=0.864), which suggests no significant association between the presence of PCF and TSH value.

Thirteen patients (27%) underwent a concurrent thyroidecstomy; 2 from Group I (20%) and 11 from Group II (28%). Of the 19 patients with PCF, 6 patients (33%) had a thyroidecstomy. Seven of 31 patients without PCF (23%) underwent thyroidecstomy. Fistula formation was not related to thyroidecstomy (p=0.508).

Twelve of the 18 patients (67%) with PCF underwent tracheoesophageal puncture (TEP). The percentage of patients was not significantly different (p = 0.753) from the 22 of 31 non PCF patients (71%) undergoing TEP.

Seventeen patients (35%) had pre-operative radiation therapy. Of these, 5 patients (29%) went on to develop a PCF. This was not statistically significantly different (p=0.438) from the 12 of 17 patients without PCF that received pre-operative radiation therapy. Twenty-five patients (51%) had post-operative radiation therapy. Of these, 10 patients (40%) developed PCF. This was not statistically significantly different (p=0.628) from the 15 of 31 patients without PCF that received post-operative radiation therapy.

Five patients each with and without PCF, 28% and 18%, respectively, underwent chemotherapy. This had no effect on the development of PCF (p=0.480).

Diabetes mellitus was identified in 9 patients (18%) pre-operatively. Of these, 5 patients (56%) developed PCF. In comparison, the other 4 diabetic patients (44%) did not develop PCF. Of the 18 PCF patients, 5 patients (28%) were diabetic and of the 31 non-PCF patients, 4 patients (13%) were diabetic, p=0.259.

The prealbumin levels were similar in both groups at 13.3 ± 5.5 mg/L and 13.4 ± 4.6 mg/L, respectively (p=0.837). These values were also similar for PCF and non-PCF groups (12.4 ± 4.2 mg/L and 14.1 ± 6.1 mg/L, p = 0.381).

\[
\text{Table 1: Risk Factors Between Euthyroid and Hypothyroid Groups.}
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<table>
<thead>
<tr>
<th></th>
<th>Euthyroid Group I (n=39)</th>
<th>Hypothyroid Group I (n=10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>59.7±11.4</td>
<td>62.9±7.7</td>
<td>0.332</td>
</tr>
<tr>
<td><strong>T</strong></td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td><strong>T3/T4</strong></td>
<td>37 (95%)</td>
<td>10 (100%)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>N0</td>
<td>30 (77%)</td>
<td>8 (80%)</td>
<td></td>
</tr>
<tr>
<td>N+</td>
<td>9 (23%)</td>
<td>2 (20%)</td>
<td></td>
</tr>
<tr>
<td><strong>Closure Technique</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staple Suture</td>
<td>9 (23%)</td>
<td>2 (20%)</td>
<td></td>
</tr>
<tr>
<td><strong>TEP</strong></td>
<td>27 (69%)</td>
<td>7 (70%)</td>
<td></td>
</tr>
<tr>
<td><strong>CP Myotomy</strong></td>
<td>20 (51%)</td>
<td>7 (70%)</td>
<td>0.478</td>
</tr>
<tr>
<td><strong>Thyroidecstomy</strong></td>
<td></td>
<td></td>
<td>0.710</td>
</tr>
<tr>
<td><strong>Flap Closure</strong></td>
<td>11 (28%)</td>
<td>5 (50%)</td>
<td>0.261</td>
</tr>
<tr>
<td><strong>Revision Surgery</strong></td>
<td></td>
<td></td>
<td>0.690</td>
</tr>
<tr>
<td><strong>Degree Diff</strong></td>
<td>36 (92%)</td>
<td>9 (90%)</td>
<td></td>
</tr>
<tr>
<td><strong>Positive Margin</strong></td>
<td></td>
<td></td>
<td>0.267</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>7 (18%)</td>
<td>2 (20%)</td>
<td></td>
</tr>
<tr>
<td><strong>Fistula</strong></td>
<td>14 (36%)</td>
<td>4 (40%)</td>
<td></td>
</tr>
<tr>
<td><strong>Misc Surg Compl</strong></td>
<td>8 (21%)</td>
<td>0 (0%)</td>
<td>0.180</td>
</tr>
<tr>
<td><strong>To1</strong></td>
<td>32 (82%)</td>
<td>8 (80%)</td>
<td></td>
</tr>
<tr>
<td><strong>EIOH</strong></td>
<td>26 (67%)</td>
<td>4 (40%)</td>
<td>0.157</td>
</tr>
<tr>
<td><strong>Illicit Drugs</strong></td>
<td>3 (8%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>7 (18%)</td>
<td>2 (20%)</td>
<td></td>
</tr>
<tr>
<td><strong>TPN/PEG ≥ 2 wks</strong></td>
<td>18 (46%)</td>
<td>4/8 (50%)</td>
<td></td>
</tr>
<tr>
<td><strong>Pre-op XRT</strong></td>
<td>10 (26%)</td>
<td>7 (70%)</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Post-op XRT</strong></td>
<td>23 (59%)</td>
<td>2 (20%)</td>
<td>0.037</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>6/37 (16%)</td>
<td>4/9 (44%)</td>
<td>0.087</td>
</tr>
<tr>
<td><strong>EBL</strong></td>
<td>372.8±291.1</td>
<td>341.7±204.6</td>
<td>0.846</td>
</tr>
<tr>
<td><strong>PKYr</strong></td>
<td>63.7±33.2</td>
<td>91.3±29.2</td>
<td>0.040</td>
</tr>
<tr>
<td><strong>TSH value</strong></td>
<td>1.6±0.8</td>
<td>7.2±6.8</td>
<td>0.0007</td>
</tr>
<tr>
<td><strong>Pre Albumin</strong></td>
<td>13.3±5.5</td>
<td>13.4±6.6</td>
<td>0.837</td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td>3.8±0.7</td>
<td>2.9±0.8</td>
<td>0.010</td>
</tr>
<tr>
<td><strong>Hgb</strong></td>
<td>13.4±2.2</td>
<td>12.5±2.3</td>
<td>0.297</td>
</tr>
</tbody>
</table>

All p-values are based on Fisher’s exact tests for categorical risk factors, and Wilcoxon rank-sum tests for continuous risk factors.

**Legend:** TEP = Tracheoesophageal puncture, CP = cricopharyngeal, Degree Diff = moderately and poorly differentiated, Misc Surg Compl = miscellaneous surgical complications, Tob = tobacco use ≥ 20 pack years, EIOH = alcohol abuse, TPN/PEG = total parenteral nutrition/percutaneous enteral gastrostomy tube, XRT = radiation, EBL = estimated blood loss, PK Yr = pack year, TSH = thyroid stimulating hormone, Hgb = hemoglobin.
Most patients (82%) were active tobacco smokers at the time of diagnosis. Eight patients (80%) were in Group I and 32 patients (82%) were in Group II (p=1.000). Of the 18 patients with PCF, 13 patients (72%) patients had an active smoking history. Of the 31 patients without PCF, 27 patients (87%) had an active smoking history. An active smoking history had no effect on the development of PCF (p=0.259).

Thirty-three patients (67%) underwent primary closure of the neogullet and the remaining 16 patients underwent pedicled or free flap closure of the neogullet. Of the 18 patients with PCF, 12 patients (67%) had primary closure. Similarly 21 of the 31 patients without PCF (68%) had primary closure.

Five patients (10%) had positive surgical margins. Three of the 18 patients with PCF (17%) had positive surgical margins. Similarly, only 2 of 31 patients without PCF (6%) had positive margins, p=0.342.

Sixteen of 18 patients with PCF (89%) with advanced stage (T3/T4) larynx cancer and only 2 patients with PCF had early stage (T1/T2) larynx cancer. All 31 patients without PCF had advanced stage larynx cancer (p=0.130). Seventy-eight percent of patients with PCF were N0. This was similar to the 77% of patients without PCF that were N0 (p=1.000). In addition, 22% of patients with PCF were N+ and 23% of patients without PCF were N+.

## Discussion

PCF formation is a troublesome and potentially devastating complication of total laryngectomy. We found a 36% PCF rate in our study of 49 total laryngectomy patients, which is consistent with previous reports [3-5,10,15]. The development of a PCF can lead to increased morbidity, delayed adjuvant treatment, prolonged hospitalization, increase in treatment costs, and is associated with an increase in mortality. As a result, it is imperative to weigh the co-morbidity risk factors for PCF development after total laryngectomy, such as low hemoglobin levels, poor nutritional status, previous radiation, previous tracheotomy, tumor site and stage, as well as the extent and technique of surgery [11].

Hypothyroidism is a frequent complication in the patients treated for head and neck cancer, with reported incidences as high as 52% [12]. Several pathophysiologic mechanisms may account for the development of hypothyroidism after treatment of head and neck cancer. Removal of the thyroid gland (or a portion of the gland) is often required to complete the oncolgic resection during laryngectomy. In addition, the blood supply to the thyroid may be compromised during the resection or during vascular access for microvascular reconstruction. Regardless of the mechanism of insult related to the thyroid gland, the literature has conflicting reports regarding the effects of hypothyroidism on wound healing.

Natori et al. [14] performed an experimental study to investigate the influence of hypothyroidism on wound healing. They induced severe hypothyroid states by performing total thyroidectomies on rat models. Wound healing of midline abdominal incisions was evaluated with assays of type-I collagen, type-III collagen, type-IV collagen, and hydroxyproline during the proliferative phase of wound healing. They found that there was a decrease in type-IV and hydroxyproline during the proliferative phase of wound healing in the presence of hypothyroidism. They concluded that a hypothyroid state constituted an important factor in delaying wound healing. Talmi et al. [13] reported a series of 4 cases where patients developed treatment-resistant PCF after total laryngectomy. Despite conservative and repeated surgical procedures, the fistulas failed to heal. After hypothyroidism was diagnosed, immediate hormone replacement therapy resulted in healing of the fistulas and a marked improvement of the patients’ general condition. In contrast, Ladenson et al. [16] studied the incidence of perioperative and postoperative surgical complications in preoperative hypothyroid patients. Of 40 patients, 17 underwent cardiac surgery while 23 had other operative procedures performed. No difference was found in the frequencies of impaired wound healing or postoperative infection between hypothyroid and control patients.

This study is the first to specifically analyze the contribution of hypothyroidism to the development of PCF formation after total laryngectomy. Our analysis of 49 patients revealed no statistically significant difference in the rate of PCF formation between Group I (hypothyroid) and Group II (euthyroid) patients. Further investigation is warranted to clarify other possible risk factors for the development of PCFs following total laryngectomy. The findings of our study further suggest that, when decided, oncologic resection of laryngeal cancer need not be delayed secondary to hypothyroid state.

Larynx preservation therapy, consisting of chemoradiation protocols, has been used with increased frequency in patients with advanced larynx cancer. Successful surgical salvage of patients with persistent or recurrent disease is a critical aspect of this organ preservation therapy. The toxic effects and complications associated with chemoradiation protocols on head and neck tissues are profound [17]. Our study did not find previous chemoradiation to have a significant effect on PCF formation. In fact, a significantly larger
number of patients with pre-operative radiation were hypothyroid (Group I), but this group had no higher incidence of PCF as compared to euthyroid patients (Group II).

We found a 13X likelihood of hypothyroidism for patients that underwent radiation therapy. These findings are similar to Gal et al. [15]. They studied 136 patients with hypothyroidism after laryngectomy and found that preoperative radiation was significantly associated (p=0.0022) with the development of hypothyroidism. In our study, however, we did not find an increased incidence in PCF in Group I compared to Group II.

We found an 83% less likelihood of having hypothyroidism for each 1 mg/L increment of serum albumin. We are uncertain of the precise clinical relevance of this finding in this patient population. A recent study by Gilles et al. [18] investigated the thyroid function in patients with proteinuria, which may be characterized by hypoalbuminaemia. Decreased levels of serum albumin, from a variety of pathophysiologic derangements, may not be fully compensated by the increased hepatic production. Similarly, there may be a concomitant decrease in other hormones and hormone-binding proteins, such as thyroid hormones and thyroxin-binding globulin (TBG).

They evaluated 159 patients with proteinuria and found that the median TSH was significantly higher in the patients than the controls (p<0.0001). Although subclinical hypothyroidism was six times more frequent in their study patients (p<0.001); overt hypothyroidism was observed in only one patient. They concluded that proteinuria did not result in overt, clinically relevant, hypothyroidism. These findings are consistent with the findings of our study that clinically relevant hypothyroidism may require a higher threshold than our current definitions of hypothyroidism (TSH above 4.5 mIU/mL).

In our study, PCF was not related to age, gender, previous radiation, staple closure, T stage or presence of cervical metastasis. These data were similarly borne out by other investigators [3,6,8,9].

The limitations of this study are those inherent to retrospective reports from a single institution. We did not evaluate each consecutive total laryngectomy candidate with a TSH level, thereby reducing the final number of study patients. Prospectively recorded data are needed for future reports to avoid any patient selection bias. Larger numbers of study patients are required to validate the results of this study.

Summary

Perioperative hypothyroidism in patients undergoing total laryngectomy is not associated with an increased incidence of PCF. A greater degree of hypothyroidism, or revised definitions of clinically significant hypothyroidism, may be required to demonstrate a significant effect on PCF formation. If planned, oncologic resection of laryngeal cancer should not be delayed secondary to hypothyroid state for concerns of post-operative PCF.

References