Protection of Laryngeal Nerve Palsy using Amniotic Membrane Shield During Thyroid Surgery

Tobias - Carling (tobiascarling@gmail.com)
Yale University School of Medicine  https://orcid.org/0000-0002-1308-187X

Research Letter

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Abstract

Recurrent laryngeal nerve (RLN) palsy, subjective voice complaints, and iatrogenic hypoparathyroidism are the main risk factors of thyroid surgery (1; 2). The rate of unintentional transient RLN injury after total thyroidectomy has been reported in up to 30% of patients, and permanent paralysis ranges between 1-5.7% (3; 4). In patients undergoing concomitant central and/or lateral node dissection, the reported incidence is even greater (5). Patients with a RLN injury typically experience dysphonia for 10-12 weeks, with approximately 8-10% having a permanent vocal dysfunction. Even in the absence of overt nerve paralysis, voice alterations can be seen in 46-84% of post-thyroidectomy patients (6; 7). Attempts to decrease the risk of nerve injury have been limited to accurate visualization and meticulous technique, performance of less extensive surgery and/or the use of nerve monitoring devices despite that their usage has never been shown to decrease RLN injury rates (8-10).

Background

Recurrent laryngeal nerve (RLN) palsy, subjective voice complaints, and iatrogenic hypoparathyroidism are the main risk factors of thyroid surgery (1; 2). The rate of unintentional transient RLN injury after total thyroidectomy has been reported in up to 30% of patients, and permanent paralysis ranges between 1-5.7% (3; 4). In patients undergoing concomitant central and/or lateral node dissection, the reported incidence is even greater (5). Patients with a RLN injury typically experience dysphonia for 10-12 weeks, with approximately 8-10% having a permanent vocal dysfunction. Even in the absence of overt nerve paralysis, voice alterations can be seen in 46-84% of post-thyroidectomy patients (6; 7). Attempts to decrease the risk of nerve injury have been limited to accurate visualization and meticulous technique, performance of less extensive surgery and/or the use of nerve monitoring devices despite that their usage has never been shown to decrease RLN injury rates (8-10).

The current study aimed at reducing the incidence of intra-operative laryngeal nerve damage with application of a protective allogeneic shield derived from human amnion and chorion membrane of the amniotic sac. The human amniotic membrane is comprised of two distinct tissues, the amnion and the chorion. Grafts derived from the amnion and chorion membrane have been used medically for over a century. Such allografts have been approved for medical uses by the FDA and with the emergence of new preservation techniques and advancements in research, they have become frequently used in various treatments (11). Since, the human amnion/chorion membrane (HACM) allograft contains growth factors, stem cells, and anti-inflammatory properties, it was hypothesized that its application may reduce RLN injury rates and negative voice outcomes.

Over a 4-month period, 58 consecutive patients (106 RLNs at risk) undergoing thyroid surgery by T.C. at Yale-New Haven Hospital were enrolled. A group of 58 consecutive patients who were operated on in the preceding months by the same surgeon having identical thyroidectomy procedures served as the historical control group (Table). The indication for surgery was malignancy in 52 of 116 (44.8%) of the cases, and concomitant central and modified radical neck dissections were performed in 43 and 13
cases, respectively. Seven patients also had primary hyperparathyroidism and thus underwent simultaneous parathyroidectomy. There was no variation in the anesthesia technique, and nerve monitoring devices were not used. The surgical technique was standardized and involved protecting all branches of the superior and recurrent or non-recurrent laryngeal nerves. The RLN is most commonly identified at its insertion into the cricothyroid muscle first and then followed caudally (tobogganing technique). However, if not detected within 10 seconds, it is identified in the tracheoesophageal groove and followed cephalad.

For patients receiving HACM, surgery was identical except for HACM being placed upon the dissected nerve as soon as possible during the operation to serve as a protective barrier from any surgical trauma and was left in place and not removed during wound closure. HACM was produced and provided by MedRex (Atlanta, GA). The allograft is shaped to cover the delicate recurrently laryngeal nerve, which has a gently curve in its upper aspect and branches in its most superior aspect. The graft was cut to length based upon the dissected nerve's length of exposure. HACM was applied with amniotic membrane orientation placed immediately upon the dissected nerve. The thyroid cartilage was digitally pulled cephalad and to the contralateral side to expose the greatest surface area of the nerve. The voice outcome (VO) was determined based on patient-reported symptoms and clinician-perceived quality is combination with objective findings on pre- and postoperative trans-nasal fiberoptic laryngoscopy, as previously described (10). Total thyroidectomy patients had serum calcium and PTH levels measured within 1-2 weeks of the operation. Any patient with a negative voice outcome was assessed clinically and by laryngoscopy until resolution. All patients provided written informed consent and the studies were approved by the local IRB.

The average age was 47.4 years in the HACM group (range 25-82 years) and 48.5 years in the control group (range 28-77 years), respectively, with females comprising 71 and 78 % in each group (all p=NS). There was no significant difference between the groups when it came to demographic factors, presence, and extent of cancer, extent of surgery, presence of lymph node involvement, or the necessity for lateral neck dissection. In no cases were there a need for intentional sacrifice of the RLN. In the HACM group there were a total of 106 RLNs dissected and at risk, whereas in the control group 94 RLNs were at risk, due to a slightly higher proportion of patients undergoing a lesser extent thyroidectomy (i.e. thyroid lobectomy) in the control group. Concordantly, there were a higher proportion of patients in the HACM group with a malignant diagnosis (33 versus 19 cases). In the HACM group, there was no cases of RLN injury, whereas 3 patients in the control group demonstrated unilateral RLN paralysis 1 week after the operation (p=0.107). All three patients had a transient RLN paralysis as evidenced by recovery of normal vocal cord function within 3 months (NS). Strikingly, subjective voice complaints (i.e. a negative voice outcome) were less common in the HACM group versus controls (1.7 vs 15.5 %; p<0.05), when they were assessed 1 week after the operation. All patients with negative voice outcomes recovered function by 3 months. Patients undergoing total thyroidectomy demonstrated normal calcium and PTH levels within 3 months follow up, and there were no cases of permanent hypoparathyroidism.
Injury to the RLN remains the most significant complication following thyroid surgery, and the morbidity includes not only aphonia or dysphonia, but the risk of aspiration, and shortness of breath (4). A person’s voice helps define our personalities and shape our ability to interact and function in society (12). Patients with voice dysfunction often report a feeling of seclusion, frustration, anxiety, fear, and depression. The rate of unintentional transient and permanent RLN injury after total thyroidectomy has been reported in up to 30% and 5.7% of patients, respectively, and is even higher in those undergoing simultaneous lymph node dissections (3-5). However, most of these studies are retrospective, self-reported, and from high-volume centers of excellence. Thus, the true incidence of nerve injury is widely believed to be at the high-end of these estimates, or possibly higher since the vast majority of thyroid surgery performed in the US is performed by low volume surgeons. Furthermore, negative voice outcomes (dysphonia and aphony) have been reported in 46-84 % of post-thyroidectomy patients (6; 7).

Amniotic membrane provides a barrier function and is a metabolically active tissue that continually remodels and grows to accommodate a growing fetus. The metabolic activities are mediated through growth factors, cytokines and chemokines that are produced by cells in the membrane (11). Growth factors present in commercially available HACM include epidermal (EGF), basic fibroblast (bFGF), keratinocyte (KGF), transforming (TGF), vascular endothelial (VEGF), and nerve (NGF) growth factors (13-16). Amniotic membrane tissue also is rich in mesenchymal stem cells and epithelial cells, which in concert with growth factors present have been shown to promote nerve, axon, and myelin regeneration in several animal models (17-19).

The results from the current study suggests that application of HACM provides a protective effect that significantly reduces the incidence of negative voice outcomes and may tend to reduce the rate of RLN injury after thyroid surgery both for malignant and benign disease. A larger multicenter trial of HACM allografts in thyroid surgery is warranted to investigate the precise indications for this novel technology.

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Tables
**Table.** Clinical characteristics of the 116 patients undergoing thyroid surgery with and without human amnion/chorion membrane (HACM) allograft.
| Characteristic                              | Allograft | Control |
|--------------------------------------------|-----------|---------|
| **Number of Patients**                     |           |         |
| Total (n)                                  | 58        | 58      |
| Female                                     | 41 (70.7%)| 45 (77.6%)|
| Age (years)                                | 47.4 ± 16.0| 48.5 ± 16.7|
| **Extent of thyroid surgery**              |           |         |
| Unilateral Thyroid Lobectomy               | 10        | 22      |
| Bilateral Total Thyroidectomy              | 48        | 36      |
| - with CND                                 | 24        | 19      |
| - with MRND                                | 5         | 8       |
| - with parathyroidectomy                    | 4         | 3       |
| **Reoperations (n)**                       | 2         | 3       |
| **Nerves at risk (n)**                     | 106       | 94      |
| **Pathology (n)**                          |           |         |
| Malignant                                  | 33        | 19      |
| - with CND (harvested LNs)                 | 5.2 ± 3.9 | 6.1 ± 2.4|
| - with CND (positive LNs)                  | 1.1 ± 1.7 | 1.6 ± 1.7|
| - with MRND (harvested LNs)                | 62.6 ± 18.3| 47.3 ± 3.4|
| - with MRND (positive LNs)                 | 14.8 ± 5.8 | 15.3 ± 5.9|
| Benign adenoma or goiter                   | 17        | 33      |
| Graves’ Disease                            | 8         | 6       |
| **Laryngoscopy (vocal cords paralyzed; n)**|           |         |
| Preoperative                               | 0         | 1       |
| Postoperative (1 week)                     | 0         | 3*      |
| Postoperative (3 months)                   | 0         | 1       |
| **Negative voice outcome (VO)**            | 1 (1.7%)  | 9 (15.5%)**|
| **Postoperative serum calcium (mg/dl)**    | 9.1 ± 0.4 | 9.1 ± 0.4|
| **Postoperative serum PTH (mg/dl)**        | 19.2 ± 8.2| 23.8 ± 12.4|
| **Permanent hypoparathyroidism (n)**       | 0         | 0       |
CND, central neck dissection; MRND, modified radical neck dissection, LN, lymph node; PTH, parathyroid hormone. Data are expressed as mean ± SD. *p=0.107 (Fisher’s exact test), **p<0.05 (Fisher’s exact test)