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Laryngeal Transplantation

Quang Luu · D. Gregory Farwell

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Abstract Loss of natural voice and the presence of a laryngostoma often stigmatizes head and neck cancer surgery patients following laryngectomy. Extensive research has been performed investigating the feasibility of laryngeal transplantation in animal models. This has thus far resulted in two long-term successful human laryngeal transplantations. The procedure is technically demanding and requires immunosuppression, but leads to considerable improvement in quality of life. Additional research into better immunosuppression and surgical techniques may make laryngeal transplantation more widespread in the future.

Keywords Larynx · Transplant · Laryngectomy · Immunosuppression

Introduction

Since the world's first solid organ transplant in 1950, physicians have continually advanced the realms of what is possible to "replace" in the body [1]. As the technical feasibility of organ transplantation became more and more established, the paradigm shifted from transplantation of organs vital to life, such as heart and lung, to organs deemed less so. Perhaps this was most elegantly demonstrated after the world's first face transplant—a medical marvel that showed the deeply positive emotional impact such surgery could make [2]. Suddenly, it was not so much what organ was necessary to live, but additionally what organs were desired to make that life worth living.

Head and neck cancer surgery patients have long lived with the stigma of laryngectomy. The loss of human voice combined with the unsightly laryngostoma often marginalized patients who had previously been fully integrated with society. Multiple articles suggest that laryngectomees suffer social isolation following surgery secondary to voice deprivation [3, 4•, 5]. Up to 87 % of patients feel stigmatized following laryngectomy, while 50 % feel "embarrassment" of having a tracheostoma [5]. It follows, then that replacement of the larynx may lead to increased quality of life in these patients.

Ethical Considerations

Although immunosuppression, and in particular cyclosporin, revolutionized transplant surgery, associated nephrotoxicity, hepatotoxicity, and increased susceptibility to secondary malignancies put patients at lifelong risk of transplant-related complications [6]. Larynx transplantation, thus, places patients into the vulnerable condition of chronic immunosuppression for what is essentially a non-vital organ (unnecessary for continuation of life). While solid-organ transplant candidates are often excluded with any history of cancer, laryngectomees with prior history of head and neck cancer have risk of recurrence as well as secondary malignancies.

Reynolds et al. queried subjects on the desirability of laryngeal transplantation when compared with double hand transplantation, heart or lung transplantation, full facial transplantation, and other scenarios using the Louisville Instrument for Transplantation (LIFT). Study patients included transplant recipients, healthy subjects, as well as

Q. Luu (✉) · D. G. Farwell
Department of Otolaryngology, University of California–Davis, 2521 Stockton Blvd Suite 7200, Sacramento, CA 95817, USA
e-mail: quang.luu@ucdmc.ucdavis.edu

D. G. Farwell
e-mail: gregory.farwell@ucdmc.ucdavis.edu

laryngectomees. Reynolds found that transplant recipients would accept the most risk from the larynx transplant procedure, while laryngectomees were least risk-tolerant. Interestingly, laryngectomees on average were willing to give up 1.2 years of life for a successful laryngeal transplant [7••]. The decision to undergo a complicated surgery with such complex ethical considerations will undoubtedly be a debate in every case considered in the future.

Background and Foundational Work

Previous researchers and clinicians have investigated the possibility of laryngeal transplantation in orthotopic animal models. Starting in the 1960s, several groups performed detailed anatomic investigations into the blood supply of canine larynges. Both autograft and allograft transplantation were performed [8, 9]. Berke et al. [10, 11] continued similar work, and used microvascular techniques to develop a canine model for laryngeal transplantation. Strome and coworkers [12–17] performed considerable investigations after introducing the rat model of laryngeal transplantation in 1992, having since published voluminous work detailing technical modifications and immunosuppression regimens contributing to allograft success. Birchall's group [18•, 19•] studied the histopathology of rejection in minipigs, concluding that the lack of strong immune response was encouraging to support future trials of laryngeal transplantation.

First Documented Successful Laryngeal Transplant

Marshall Strome et al. performed the world's first laryngeal transplant in 1998 in a 40 year-old patient who had previously suffered irreparable traumatic injury to the larynx. Aside from mild hypertension, the patient was healthy. He underwent extensive preoperative evaluation by a psychiatrist as well as multiple members of the surgical team. The donor was a human leukocyte antigen-matched patient who had been intubated for less than 48 h. The donor larynx included six tracheal rings and the thyroid and parathyroid glands. The right and left superior and right inferior laryngeal nerves were anastomosed, while the recipient left recurrent laryngeal nerve was not identified [20].

At 4 months electromyography confirmed reinnervation of the vocal folds and cricothyroid muscles, and by 36 months his voice sounded normal. He had return of thyroid and parathyroid function.

The patient was fed via gastrostomy tube for 14 weeks, and then resumed oral intake. Immunosuppression was maintained with cyclosporine, mycophenolate mofetil, and prednisone. Biopsies taken of tracheal mucosa at several timepoints revealed no evidence of rejection.

UC Davis Patient

Our transplant patient was a unique, ideal patient. She was a 51 year-old woman with an 11-year history of laryngeal trauma and subsequent complete stenosis from intubations and traumatic extubations following an episode of renal failure. Despite attempts at repair, she was left a laryngeal cripple with total stenosis of her glottis and proximal subglottis. She had already undergone a kidney-pancreas transplant which necessitated lifelong immunosuppression with tacrolimus and leflunomide. Thus, her laryngeal transplant conferred what was felt to be minimal additional risk from an immunologic standpoint. After extensive preoperative counseling and preparation by the surgical team, a 38 year-old suitable donor was found.

Technical Details

Farwell et al. [21••] previously reported the technical details of her surgery, but they will be briefly elucidated here. The transplant donor was harvested first, with care taken to perform early isolation of the great vessels and nourishing branches to the laryngotracheal complex. The larynx was harvested with the thyroid and parathyroid glands. Once donor vessels were deemed adequate intraoperatively, the recipient was induced with anesthesia and a narrow-field laryngectomy was performed (see Fig. 1a). Meticulous care was taken to isolate the bilateral superior laryngeal nerves, superior thyroid arteries, transverse cervical arteries, bilateral recurrent laryngeal nerves, and great vessels of the neck. The harvested larynx was perfused with 3 L of University of Wisconsin perfusate (DuPont Pharma, Wilmington, DE, USA).

The donor larynx's right pharynx was sewed into the recipient bed. Immediately anastomoses were then performed between the donor right superior thyroid and recipient superior thyroid artery. The donor right brachiocephalic vein was anastomosed with the recipient internal jugular vein. Blood flow was then established. Microneurography of the bilateral superior laryngeal nerves and right recurrent laryngeal nerves was performed. The adductor branch of the donor left recurrent laryngeal nerve was sutured to the recipient ansa cervicalis, and the left donor recurrent laryngeal nerve was sutured to the recipient left phrenic nerve in end-to-side fashion. Additional right and left-sided vascular anastomoses were performed between the donor inferior thyroid arteries and the

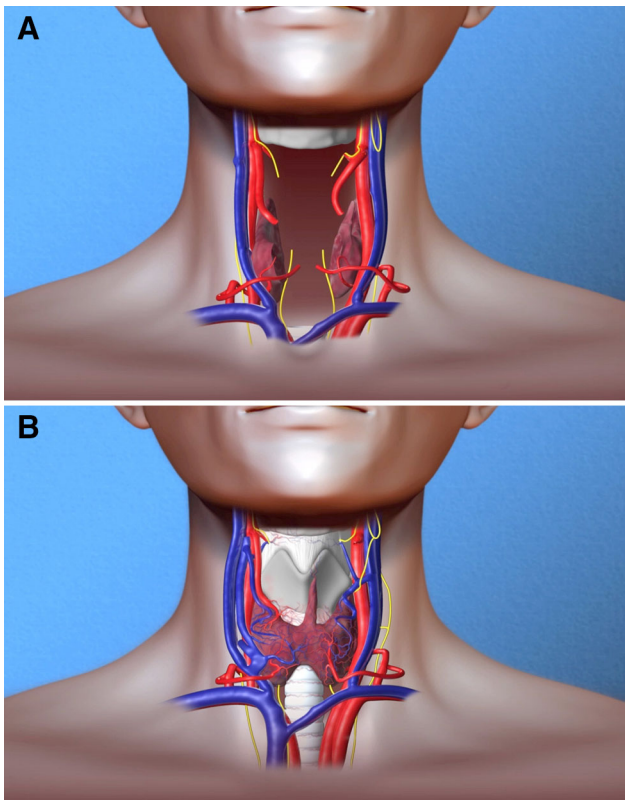

Fig. 1 Schematic of larynx transplant recipient following narrow-field laryngectomy (**a**) and after transplantation of donor larynx (**b**)

transverse cervical arteries and the donor middle thyroid vein, and the recipient left jugular vein (see Fig. 1b). Eight rings of donor trachea were used. The wound was then closed with passive drains. Primary closure was deemed risky given excessive wound tension. She was returned to the operating room the following day for delayed closure.

Postoperative Course

The patient was given immunosuppression managed by the medical team (detailed elsewhere in this text) and recovered from her surgery without incident. She has had biopsies taken on postoperative days 1, 14, 30, and 137, all showing normal-appearing laryngeal mucosa. She has started on a liquid diet. Given her lack of laryngeal adduction, it was decided not to decannulate her. She has been extremely happy with her more "natural" voice. In her own words, "This operation has restored my life." "I've been smelling food like crazy," she gushed. Her newfound ability to project a less "robotic" voice, the return of taste, and the return of her sense of smell have dramatically improved the quality of her life.

Future Directions

The two reported successful larynx transplants were undoubtedly impressive achievements of multidisciplinary effort. Yet although technically feasible, several concerns exist. Both cases occurred in patients who previously had no prior open neck surgery. The laryngectomee has often undergone prior neck lymphadenectomy with attendant ligation of possible recipient arteries and veins. Furthermore, neither larynx transplant patient had a history of prior cancer, eliminating the concern for recurrence of laryngeal cancer. Finally, the difficulty in decannulating patients safely, along with no documented return of vocal cord adduction, begs the question of how much "functionality" a larynx transplant truly receives.

Significant adduction of the vocal cords following transplantation has yet to be achieved. The successful reinnervation as documented by EMG, although positive, has not translated into strong vocal cord abduction. Future research is necessary and current studies investigating cross innervation from the phrenic nerve or ansa cervicalis are awaited with great anticipation. Selective reinnervation of adductor and abductor branches of the laryngeal nerves may allow inspiratory abduction. Significant clinical success, however, is slow to manifest [22].

Immunosuppression is another area in which advances will aid the success of future laryngeal transplantation. This topic is explained in a separate chapter elsewhere in this text.

Conclusion

Long-term successful laryngeal transplantation in humans has now been documented twice. The recent explantation of the original transplant at the Cleveland Clinic for chronic rejection (Robert Lorenz, personal communication; also presented at the American Academy of Otolaryngology meeting in Vancouver 2013) is a sobering reminder of the inherent complexities in undertaking such a procedure. However, perhaps to many patients, the requisite lifelong surveillance is worth the risk: Dr. Lorenz showed video of the patient expressing desire for a second laryngeal transplant because of the improvement in quality of his voice after the original surgery. The recent working party report from the Royal College of Surgeons best summarizes the necessities involved: laryngeal transplantation absolutely requires the expertise of a multidisciplinary team, and must involve the patient in the complex process of weighing the risks and benefits of this procedure [23]. Thus far, laryngeal transplantation has occurred in its own microcosm of ideal factors, but as refinement of immunosuppression

and surgical techniques continue, it may see more widespread application.

Compliance with Ethics Guidelines

Conflict of Interest Quang Luu and D. Gregory Farwell declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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