Combined Thyroid-Parathyroid Organ Transplantation: Demonstration of Technical Feasibility in a Perfused Cadaver Model

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New surgical procedures are traditionally developed using animal models.[1,2] Despite their usefulness, these models often fail to replicate human anatomy, whereas cadavers lack the fidelity of perfused human tissue. Perfused cadaver models have been developed for surgical education and are used to simulate a range of vascular procedures for training purposes.[3] Previous studies have compared the models favorably to living humans in fidelity of tissue characteristics and bleeding.[3,4] However, such models have not been used routinely to develop new surgical procedures. We sought to assess the technical feasibility of a combined thyroid-parathyroid organ transplant (T-POT) using a perfused cadaver model.

Total thyroidectomy is performed for both benign and malignant thyroid disease, with more than 100,000 estimated total thyroidectomies performed in the US each year.[5] Total thyroidectomy is typically well tolerated with infrequent but life-altering complications. Permanent hypoparathyroidism is a recognized complication of thyroidectomy, with rates up to 3% or higher after thyroid surgery.[5] The estimated prevalence of post-thyroidectomy hypoparathyroidism is 25 per 100,000 persons in the US[6] and 0.8 to 27 per 100,000 persons worldwide.[7]

Chronic hypoparathyroidism causes a significant burden of healthcare utilization, morbidity, and a decrease in quality of life.[7-10] Renal comorbidities, including chronic kidney disease and renal failure, are especially pronounced.[7] Even patients with normal-range biochemical values on stable regimens for hypoparathyroidism report ongoing symptoms and poorer global complaint scores and quality of life than controls.[9,10] Although studies have been mixed, some population database studies report increased mortality in patients with chronic hypoparathyroidism.[11] It is increasingly appreciated that current pharmacologic treatments for chronic hypoparathyroidism, which fail to replace the underlying regulatory hormonal axis, are likely inadequate for many patients. Use of recombinant parathyroid hormone (PTH) analogues has been explored in the short term but does not afford minute-to-minute physiologic control of serum calcium.[10] Concurrent hypothyroidism has been shown to worsen symptoms of chronic hypoparathyroidism.[12]

Transplantation of vascularized parathyroid tissue in aparathyroid patients could allow for physiologic regulation of calcium homeostasis and offer an alternative option for disease management in patients whose hypoparathyroidism is life-altering and refractory to medical treatment. Combined en bloc thyroid-parathyroid heterotopic allotransplantation is a potential treatment for such carefully selected patients and could also alleviate concurrent hypothyroidism. We sought to demonstrate the technical feasibility of such a transplant. Using a perfused cadaver model, we performed an en bloc thyroid lobectomy and parathyroidectomy with microvascular anastomosis to the thoracodorsal vessels in the axilla and demonstrated perfusion to the graft.

METHODS AND RESULTS

Experimental model

This experiment was performed to assess technical feasibility in a nonliving human model that retained the ability to prove perfusion to an engrafted thyroid-parathyroid organ as a measure of technical success. A male perfused cadaver model was used (MAXFI Surgical Simulations, Columbia, MO). These cadavers are fresh

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and not embalmed. The cadaver was inspected before beginning and confirmed to have no evidence of previous neck or axillary surgery. Preparation of the perfused cadaver entails open thrombectomy and cannulation of great vessels with the infusion of a blood substitute via a pulsatile motor. The operative team included a surgical oncologist, a plastic and reconstructive surgeon with expertise in microvascular surgery, and an abdominal transplant surgeon.

Procedure

The cadaver was positioned in a modified Fowler position with the left arm abducted to expose the axilla. Perfusion of the cadaver was performed via the femoral artery. A standard left thyroid lobectomy with en bloc removal of perithyroidal soft tissue and parathyroid glands was performed. The superior thyroid, inferior thyroid, and lower pole vascular pedicles were sequentially isolated and dissected distally to provide several centimeters of length for anastomosis. This cadaver had no left middle thyroid vein. The left inferior thyroid artery was bifurcated before insertion into the thyroid gland, and the common trunk was isolated and marked. The thyrothymic ligament was divided at the thoracic inlet. Candidate parathyroid glands were identified in situ but dissection intentionally was limited. Generous margins of soft tissue were preserved around the thyroid gland, and minimal dissection was undertaken on the posterior surface of the thyroid gland to ensure an en bloc thyroid-parathyroid specimen. The entire left hemithyroid was removed from the anterior trachea, and the isthmus was divided using electrocautery and the vascular pedicles were ligated and divided sharply. On the back table, the candidate vessels for anastomosis were cleaned in preparation for implantation (Fig. 1).

Simultaneous with the thyroid lobe procurement, a separate team prepared the recipient site in the left axilla. An incision was made in the left anterior axillary line inferior to the border of the pectoralis major and carried down to the chest wall. The thoracodorsal nerve, artery, and vein were identified and isolated beginning at the scapular border and tracing over the serratus anterior (Fig. 2). Once the graft was prepared, the thoracodorsal vessels were individually clamped, clipped distally, and divided, and robust perfusion was demonstrated through each with bleeding when clamps were released. The surgical microscope was brought onto the field along with the autograft. A single end-to-end arterial anastomosis was created between the inferior thyroid artery and the thoracodorsal artery using interrupted 8-0 suture. An end-to-end venous anastomosis was created using a draining lower thyroid pole vein and the thoracodorsal vein using a 2-0 microvascular coupler.

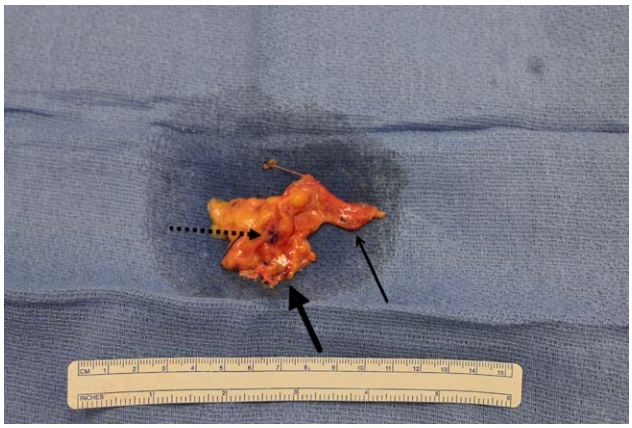


Figure 1. Left thyroid lobe with en bloc parathyroid and thymic tissue, after back table preparation for transplant. The specimen is oriented with the superficial surface visible and superior thyroid pedicle at image right. Indicators mark the superior thyroid pedicle (thin arrow), the inferior thyroid artery (thick arrow), and a large lower thyroid pole vein (hatched arrow).

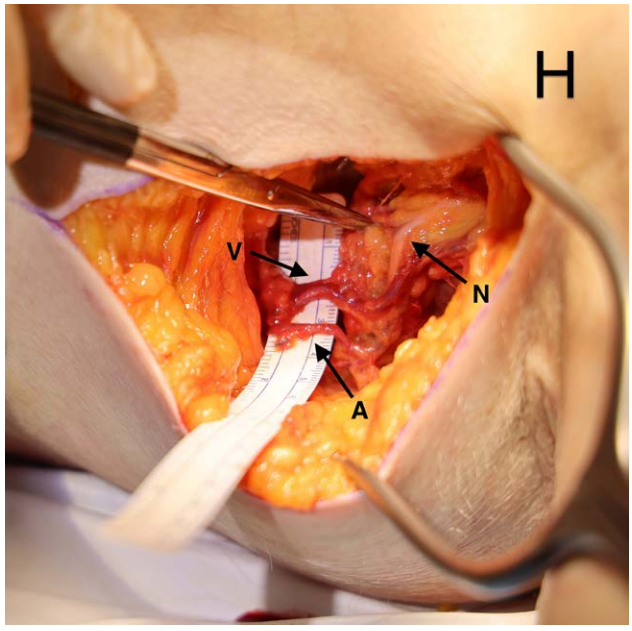


Figure 2. Recipient site in the left axilla, prepared for transplant. The thoracodorsal artery (A, arrow 1), vein (V, arrow 2), and nerve (N, arrow 3) are shown. H marks head at image right.

The graft was ensured to lie without tension in the axillary pocket (Fig. 3). After completion of the thyroid-thoracodorsal anastomoses, the systemic blood pressure was increased using the perfusion system and the thyroid gland was noted to bleed robustly at 1 hour after transplant (see Video [online]), demonstrating successful perfusion of the en bloc thyroid-parathyroid autograft when implanted into the axilla. Owing to the technical limitations of the

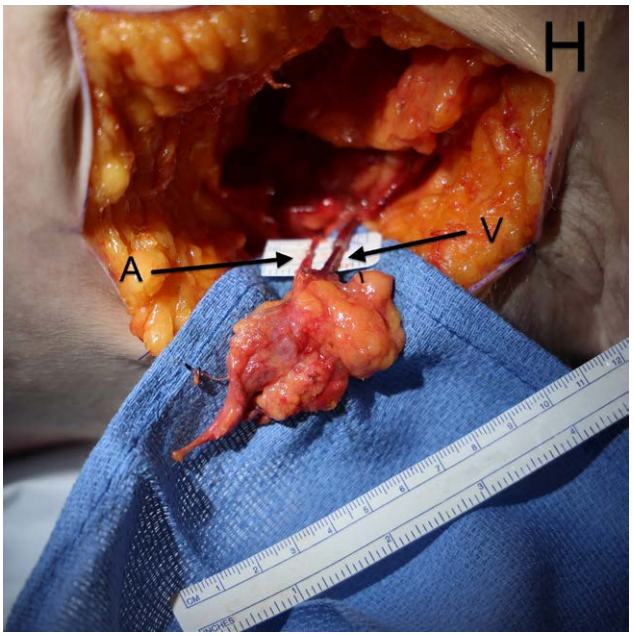


Figure 3. Thyroid-parathyroid organ transplantation specimen after completion of vascular anastomoses in the axilla. Anastomoses are splayed for identification and indicated as arterial (A) and venous (V), with head (H) at image right.

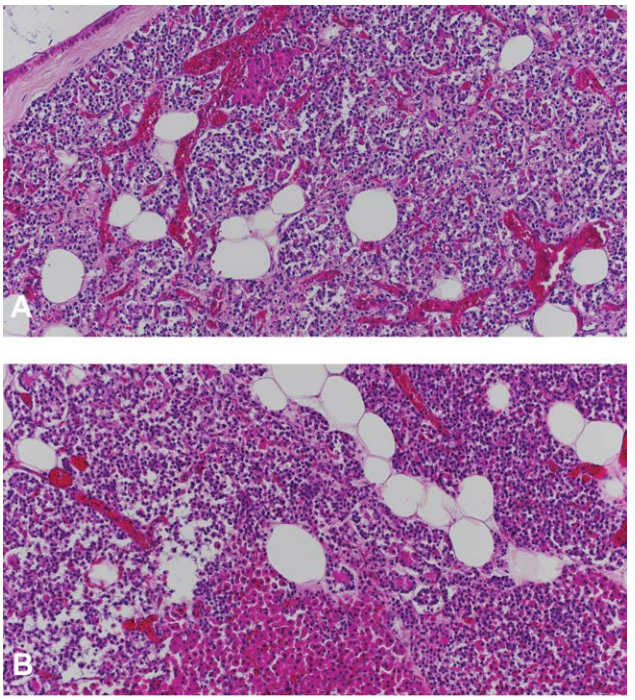


Figure 4. Histologic examination of parathyroid glands within the thyroid-parathyroid organ transplantation specimen after explantation: (A) autotransplanted superior and (B) inferior parathyroid glands.

perfused cadaver model, the perfusion of parathyroid glands in situ was not demonstrated. Histologic examination of formalin-fixed explanted graft revealed parathyroid tissue in 2 locations: adjacent to the inferior thyroid artery on the posterior aspect of the thyroid lobe and within the thymic tissue included in the en bloc specimen (Figs. 4A, 4B).

DISCUSSION

Hypoparathyroidism can be a troublesome complication of thyroidectomy, requiring lifelong supplementation of calcium and calcitriol with frequent need for healthcare utilization to titrate medication and manage symptoms. As many as 79% of patients with chronic hypoparathyroidism reported a related emergency room visit or hospitalization in the previous year and 20% reported a disease-related change in employment.[8] Over time patients with chronic hypoparathyroidism are at risk for nephrocalcinosis and nephrolithiasis, as well as cardiac, ophthalmologic, and psychiatric comorbidities.[7] Combined hypoparathyroidism and hypothyroidism are particularly problematic, with deficits in postural stability and muscle strength and function not observed in patients with hypothyroidism alone.[12] Notably, surveyed patients indicate they are motivated to pursue invasive experimental treatments in hopes of a cure of their hypoparathyroidism, valuing a cure to their hypoparathyroidism as worth trading a median of 3.6 years of life.[9]

Hormone replacement approaches to treat chronic hypoparathyroidism include injectable PTH analogues and parathyroid transplantation. Recombinant PTH (Natpara; Takeda Pharmaceuticals USA, Inc, Lexington, MA) was initially approved for the treatment of chronic hypoparathyroidism, but is associated with significant side effects, has a risk of osteosarcoma, and has been recalled due to safety concerns.[10,13,14] The safety and efficacy of palopegteriparatide (TransCon PTH; Ascendis Pharma Inc, Palo Alto, CA), a newly developed prodrug of PTH, has not been demonstrated and the drug has not been approved by the FDA.[15] Historically, the risks and side effects of chronic immunosuppression have been thought to outweigh the benefits of physiologic PTH replacement by allogeneic parathyroid transplantation in chronic hypoparathyroidism. However, improvements in and better tolerance of modern immunosuppressive regimens combined with new understanding of the morbidity of chronic hypoparathyroidism have made the prospect of parathyroid transplantation more appealing.[16,17] Success of en bloc parathyroid allotransplantation has not been rigorously evaluated.

Parathyroid gland autotransplantation, initially developed by Halsted,[1] is an effective approach to minimize

the risk of hypoparathyroidism during thyroidectomy.[18] Parathyroid gland allotransplantation is a conceptually attractive option to restore parathyroid function in patients with chronic hypoparathyroidism. As with autotransplantation, this approach uses minced parathyroid glands from related or unrelated donors placed into a recipient muscle bed with reliance on neovascularization for engraftment.[17,19,20] Systematic reviews have estimated success rates, defined as a significant decrease in need for calcium supplementation, of approximately 41% to 46% at 1 year using this approach.[14,21] Graft survival rate for minced parathyroid allotransplantation varies widely, from 18.7% at a mean of 7.3 months to 81.8% at 20 months, and appears to be positively influenced by peri-transplant immunosuppressive therapy.[22] Studies of combined living-related parathyroid and thymus allotransplantation in patients with DiGeorge syndrome have found improved graft retention in patients with HLA2 matching.[23] Overall, graft retention and function of minced parathyroid allografts remain unsatisfactory, and immunosuppression seems to remain an important part of graft survival in these allotransplants.[14,21]

Animal studies of parathyroid transplantation have shown superior results when a vascularized gland rather than the minced technique is used for parathyroid transplantation.[24] Human transplantation of en bloc fetal thyroid/parathyroid vascularized allografts from deceased human donors into hypoparathyroid adults has been reported with mixed results.[25-28] Thyroid autotransplantation alone using microvascular anastomoses has been performed for the prevention of radiation-induced hypothyroidism in patients with head and neck cancer; however, the parathyroid glands were not autotransplanted.[29,30] Heterotopic allotransplantation of vascularized adult thyroid-parathyroid organs has not been demonstrated. This report of the technical feasibility of T-POT represents the first step toward this goal.

Our goal is to develop transplantation of the intact parathyroid gland, preserving the native blood supply by microvascular anastomosis. Our T-POT approach relies on maintaining the blood supply by transplanting the thyroid-parathyroid glands en bloc, which can be achieved by transplanting either a thyroid lobe with 2 or the total thyroid with 4 attached parathyroid glands. We view these strategies as complementary and envision using them selectively based on clinical circumstances. The donor lobectomy approach is amenable to living donor organ donation, which may have immunologic advantages.[23] The decision for this approach must weigh potential donor morbidities such as recurrent laryngeal nerve injury and post-lobectomy hypothyroidism. The donor total thyroid approach would be suitable for deceased donors and would provide greater endocrine tissue to potentially restore both parathyroid and thyroid function.

Our use of a perfused human cadaver model to establish technical feasibility of T-POT is noteworthy. Perfused cadavers have been used predominantly for training in vascular and general surgery, with consistently positive data for tissue quality and fidelity of dissection and bleeding across trauma surgery,[3,4] neurosurgery,[31] and vascular surgery.[32] Importantly, the use of perfused cadavers for simulation of microvascular anastomosis has been previously demonstrated, with successful cadaveric microvascular flap transfer, vessel bleeding, and positive indocyanine green angiography at the skin and microvasculature in these models.[33,34] We noted robust bleeding of small vessels and parenchymal organs during dissection of the donor thyroid lobe and axillary bed, and excellent quality of tissue handling with strong fidelity to living human tissue. Importantly, we demonstrated robust bleeding of the thyroid-parathyroid organ specimen after microvascular anastomosis showing the technical feasibility of this approach. Proof of parathyroid gland perfusion will require in vivo visualization (eg indocyanine green angiography) and ultimately by demonstration of sustained physiologic function in the recipient. Our future work to develop T-POT clinically will address these technical aspects of T-POT as well as important immunologic and physiologic parameters of endocrine function.

Author Contributions

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Methodology: Martens, Awad, Sacks, Olson
Conceptualization: Sacks, Olson
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