Review Article

Ushering in the era of penile transplantation

Alison M. Rasper, Ryan P. Terlecki

Department of Urology, Wake Forest Baptist Health, Winston-Salem, NC, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Ryan P. Terlecki. Department of Urology, Wake Forest Baptist Health, Winston-Salem, NC, USA. Email: rterleck@wakehealth.edu.

Abstract: Penile transplantation is a novel approach to management of penile loss in the developing field of composite tissue allotransplantation (CTA). Prior management for significant penile loss has been free flap phalloplasty with issues related to function, cosmesis, and functional loss from the location of flap harvest. Transplantation has been an evolving field with advancement in CTA over the past several decades leading to the option of penile transplant. Management of penile injury with replantation provided some preliminary groundwork on the technical aspects for penile transplantation. Additionally, penile transplantation raises many ethical, emotional, and psychological considerations with need for patience amidst ongoing advancement within the field.

Keywords: Composite tissue allotransplantation (CTA); penile reconstruction; penile transplantation

Submitted Aug 24, 2016. Accepted for publication Aug 30, 2016.
doi: 10.21037/tau.2016.11.02
View this article at: http://dx.doi.org/10.21037/tau.2016.11.02

Background

Transplantation conceptually dates back to archeologic records from thousands of years ago with dramatic advancement over the past sixty years (1). Early attempts at solid organ transplantation were met with graft rejection, as knowledge of immunology was still rudimentary. In 1936, Russian surgeon Yuriy Voronoy performed a renal transplant with ABO incompatibility, which failed to produce urine and the recipient died two days later (1). From 1951–1952, David Hume and colleagues at Brigham Hospital in Boston performed nine renal transplants, with each resulting in allograft rejection (1). In 1954, Murray and Merrill performed the tenth renal transplant at Brigham Hospital from an identical twin donor, and the graft remained functional until recurrent glomerulonephritis nine years later (2,3). Initial immunosuppression was attempted with whole body radiation, which led to severe side effects resulting in death after transplantation (4). In the late 50's, pharmacologic advances lead to the evaluation of 6-mercaptopurine in animal studies (5). However, even at decreasing doses the drug was found to be toxic in human transplant patients (6). A breakthrough for solid organ transplantation in the 1960's was the development of azathioprine. When used in combination with corticosteroids for solid organ transplantation, it facilitated host tolerance and decreased rejection (7).

Soon after kidney transplantation, liver transplantation was developed and was met with technical challenges. One year survival was poor, similar to renal patients, due to the immunocompromised state (8). Initial cardiac, pancreatic, and pulmonary transplantations occurred in the late 1960's with poor long-term success (9). Further discovery of immunomodulation, with development of the calcineurin inhibitors, lead to improved graft and patient survival from the mid-1980's through present day (9). Additionally, this period correlated with the discovery and further understanding of the role of major histocompatibility complex (MHC) and human leukocyte antigens (HLA) in transplantation (10).

Successful efforts in solid organ transplantation spawned interest in composite tissue allotransplantation (CTA). The United Network for Organ Sharing (UNOS) defines a CTA as having the following criteria: (I) vascularized and

requires blood flow by surgical connection of blood vessels to function after transplantation; (II) contains multiple tissue types; (III) is recovered from a human donor as an anatomical/structural unit; (IV) is transplanted into a human recipient as an anatomical/structural unit; (V) is minimally manipulated; (VI) is intended for homologous use; (VII) is not combined with another article such as a device; (VIII) is susceptible to ischemia, and therefore, only stored temporarily and not cryopreserved; and (IX) is susceptible to allograft rejection, generally requiring immunosuppression (11). Several types of human CTA have now been performed including hands, arms, face, knee, larynx, and, most recently, penis.

Surprisingly, renal autotransplantation was first performed nearly a decade after the initial work with renal allotransplantation. Hardy first described successful renal autotransplantation in 1963 for high ureteral injury (12). This technique was then used for additional indications such as renal arterial pathology requiring benchwork repair of the vasculature prior to autotransplantation. In 1990, Novick *et al.* reported a series of 108 renal autotransplantations for renal artery disease, ureteral replacement, and renal cell carcinoma (13).

Unlike renal transplantation, penile replantation preceded allotransplantation. Penile loss is rare and occurs in various ways. These include self-inflicted, or Klingsor syndrome, often associated with situations involving schizophrenia, low self-esteem, religious conflict, guilt, or unresolved transsexual issues (14). Other reports have included work related accidents (15). In the 1970's, there was an epidemic of wives performing penile amputation in Thailand as punishment for infidelity (16). Iatrogenic injuries following circumcision are typically distal and more common among the pediatric population in the United States. However, some African cultures perform circumcision rituals as initiation into manhood and concomitant injury has been reported (17). An additional iatrogenic source is oncologic treatment for large, invasive penile squamous cell carcinomas with surgical penectomy. Finally, genitourinary injuries may result from penetrating and blast trauma both within both the civilian and military population. Review of the Department of Defense Trauma Registry from October 2001 through August 2013 found 1,367 service members with genitourinary injuries, with 31% involving the penis (18).

Penile replantation

Penile replantation was first reported in 1929 by Ehrich *et al.*, featuring a macroscopic technique in which no neurovascular anastomoses were performed (19). This macroscopic technique led to poor results with eventual skin loss. Their approach included anastomosis of the urethral mucosa, corpora spongiosum, and tunica albuginea of both corpora cavernosa in a watertight fashion. Microscopic penile replantation was first reported in 1976 with improved outcomes (20). In 2004, Landstrom *et al.* reviewed the cases of complete penile transection and replantation (21). The review included 28 cases with 16 suffering complications, of which 14 had preputial loss. The number of penile arteries and veins required for perfusion is controversial, with the review supporting the need for repair of least one dorsal artery. One case omitted dorsal arterial anastomosis, and despite anastomosis of two profundi arteries, the operation resulted in necrosis of the glans and foreskin (20). Anastomosis of the arteries should be performed first to allow for reduction in ischemia time. The role of cavernosal artery anastomosis is controversial. In the Landstrom *et al.* review, 3 of 6 patients had erections with cavernosal artery anastomoses compared to 15 of 22 without cavernosal artery approximation (21). Some argue that the vascular flow provided by the cavernosal arteries is low and prolonged operative time to perform this maneuver can lead to further damage to erectile tissue. Venous outflow is essential for limiting postoperative edema and to promote preservation of skin with some advocating maximizing the number of attainable superficial and deep venous anastomoses (22). Anastomosis of the dorsal nerve is performed subsequent to reestablishing vascular flow. Perioperative management of replantation includes antibiotic coverage, anticoagulation, use of hyperbaric oxygen, penile immobilization, and wound care.

Penile transplantation

Penile transplantation has been demonstrated in animal models. In one study, penises from Brown-Norway rats were removed and placed in an omental pouch of Lewis rats immunosuppressed with FK506 (tacrolimus), with absence of rejection on pathology (23). Another study involved penile transplantation between Beagles with microvascular anastomoses of neurovascular structures (24). The dogs were maintained on a regimen of FK506, mycophenolate mofetil (MMF), corticosteroids, and antibiotics. Catheters were removed on day 7 with voids recorded. On day 14, the transplanted penises were resected for pathologic review. Among 20 transplants, venous and arterial anastomoses

were successful in 95% and 87.5%, respectively. Significant swelling was noted in every case, with three cases experiencing glans necrosis. Urination was normal in all subjects, and cystourethrography on day 10 confirmed universal absence of stricture. Pathology confirmed patent vasculature, limited infiltration of inflammatory cells, and absence of interstitial necrosis.

Guangzhou General Hospital in China reported the first human penile transplantation in 2006 (25). The recipient was a 44-year-old male with a history of traumatic penile amputation eight months prior, and the organ was from a 22-year-old brain-dead donor. The parents of the donor provided consent, the donor and recipient were crossmatched for HLA, panel reactive antibodies and blood type, and approval was obtained from the hospital's ethical committee. The urethral mucosa was re-approximated, followed by corpora spongiosum, and the tunica albuginea of both corpora cavernosa. The deep dorsal vein, dorsal artery, and dorsal nerve were then reconstituted, followed by the superficial dorsal vein after closure of Buck's fascia. Induction included daclizumab, MMF, and methylprednisolone. The maintenance regimen consisted of MMF, prednisone, and cyclosporine. Venous stasis and edema resulted in loss of the distal penile skin. The urethral catheter was removed on postoperative day 10. On postoperative day 14, the patient and his wife requested graft removal due to psychological concerns based on aesthetic appearance. Pathology confirmed absence of rejection.

This initial report prompted ethical concerns. The treating hospital subsequently released 10 principles for penile transplantation after case review (26). These included defining the target population, as well as the need to establish protocols and a review board for each case inclusive of a multidisciplinary team of surgeons, transplant specialists, pharmacists, and psychological support for recipient and partner. Thorough preoperative evaluation and informed consent for donor and recipient were also deemed essential.

The next incidence of human penile transplantation was performed in December 2014 at Tygerberg Hospital in South Africa. The patient was a 21-year-old male with penile loss due to complications from ritual circumcision. This problem afflicts approximately 250 South African men annually resulting in psychological distress and even contemplation of suicide (27). The 9 hour operation was led by Dr. Andre van der Merwe. This was reportedly challenging due to extensive fibrosis and disruption of native vasculature. The dorsal nerve was successfully reconstituted. The dorsal artery of the graft was fed by the recipient's inferior epigastric and superficial external pudendal arteries (27). Postoperatively, additional procedures were required secondary to thrombosis of the penile artery, an infected hematoma, and development of urethral fistula. It has been reported that the recipient had psychological improvement, intact skin sensation, and erectile function (28). It was also stated that natural conception was achieved, although this resulted in stillbirth (28).

In May 2016, surgeons at Massachusetts General Hospital in Boston reported success with penile transplantation in a 64-year-old patient who previously underwent penectomy for penile cancer (28). Reports state the recipient had been cancer free for several years. The procedure took 15 hours and involved the participation of 13 surgeons (28). An episode of rejection was treated without complication (28). Sexual function is yet to be determined, but normal voiding was confirmed upon removal of catheter 3 months postoperatively (28).

Perioperative management

Perioperative management of penile transplantation requires a multidisciplinary approach. Donors should be screened for EBV, CMV, hepatitis B and C, and HIV serology (29). Additionally, close examination for penile lesions is necessary in an immunocompromised recipient. ABO and HLA compatibility should be assessed to prevent rejection. It is unclear if immunosuppression will need to be lifelong. Rates of rejection for CTA exceed that of solid organ transplantation due to the antigenic contribution of skin. Acute rejection of CTA has been reported in an excess of 85% (30). Immunosuppression for CTA mirrors that of solid organ transplants. Induction involves antithymoglobulin, daclizumab, basiliximab, alemtuzumab, or high dose steroids. Maintenance immunosuppression is typically a combination of MMF, prednisone, and FK506.

Postoperative wound care involves attention to edema and signs of impending skin loss. Biopsy may be required to determine need for adjusting immunosuppression. Chronic rejection of CTA is also a concern. This process targets the skin and deep vessels, potentially resulting in dermal sclerosis and graft loss (31). In patients who regain potency, monitoring of erectile function may allow detection of chronic rejection secondary to corporal fibrosis.

Subsequent clinical evaluations should also assess voiding

function. One of the goals should be to restore the ability to void in a standing position. Review of penile replantation series demonstrates a 6.7% incidence of urethral complications (32). Development of urethral stricture disease or fistula may require additional procedures.

Recovery of erectile function will depend on numerous factors. These involve the neurovascular status of the recipient, the state of the donor organ, surgical technique, and subsequent healing. In addition to evaluation of sexual function, psychological support should be provided to both patient and partner.

Optimization of the hormonal milieu and use of medications such as phosphodiesterase-5 inhibitors may be required. In patients with replantation, placement of a penile prosthesis has typically been delayed until return of sensation (32). Infectious precautions are paramount when considering prosthesis placement in an immunocompromised patient.

Ethical considerations

Penile transplantation includes medical, cultural, emotional, and even religious concerns. As with other CTA, penile transplantation is a quality-of-life, rather than a life-saving procedure. Medical considerations involve the screening and immunosuppression previously described. Immunosuppression in patients with a history of penile cancer raises concerns, and optimal cancer free interval may need to be determined. Most transplantation protocols require recipients to be free of solid organ and skin cancer for 2–5 years prior to listing (33). Immunosuppression increases the risk of bacterial and viral infections, as well as that of secondary malignancies. In light of this, considering a quality-of-life procedure that may threaten patient longevity, a detailed risk benefit analysis is essential. Additionally, the threshold to remove the transplanted organ should be discussed preoperatively.

Emotional concerns involve not only the recipient and his potential partner(s), but also the parties involved in consideration of organ donation. Some families view donation for CTA as mutilation, and there may be a social stigma associated with the donation of genitalia of a family member. Studies involving CTA have shown that the general public is unaware that the face and hands can be donated, and the question will also need to be posed as it relates to genitalia (34). A New Jersey study of 1,000 individuals noted a greater willingness to donate solid organs over either hand or face (35). Awareness and public education regarding donation for CTA is critical.

Detailed psychosocial assessment of potential recipients and their respective partners appears to be essential. The outcome of the case in China demonstrates the need for proper counseling and informed consent (26). There is also a need for privacy despite the interest by the media. Patients are likely to require social support and should be assessed for the ability to cope with the possible stigma and even publicity. It is understandable how this may be especially challenging with receipt of a sexual organ as opposed to a solid intraabdominal organ.

Religion and culture play an especially interesting role in penile transplantation for donors and recipients. The question of sexual sin is unique to this form of transplantation, and some may view such sin as being passed with the genitalia. Christianity asserts the role of caring for the sick and dying, lending itself to the support of organ donation. However, in 2009, Pope Benedict XVI wrote an open letter that included the prohibition of transplantation of gonads and organs connected to personal and procreative identity (36). Muslim scholars differ on the Islamic definition of brain-death (37). However, the Islamic position is that organs responsible for fertilization and satisfying sexual desire should not transferred from one human to another (38). Conservative and Reformist Judaism encourage organ donation, and there is no clear consensus of brain-death among orthodox leaders (39). Organ donation has been part of Hindu myths and writings without clear discussion related to genitalia (40). Buddhism and confucian ethics debate the time of death and the role of a lingering spirit afterwards, making the concept of donation somewhat complicated (41,42).

Future considerations

Further application of penile transplantation raises the possibility of considering more controversial patient populations, such as those with congenital micropenis or those considering sexual reassignment. This raises additional ethical questions as well as technical postulation of feasibility in transplanting a male phallus to a female recipient. Additionally, patients that have suffered traumatic blast injuries, as seen in wounded members of the military, may present a formidable challenge due to significant disruption of the neurovascular anatomy within the pelvis.

As we move forward within an era full of promise, patience is a virtue of the utmost importance. Failures will be encountered but should not deter investigation of

what is likely to be an operation which provides dramatic improvement in quality of life among properly selected individuals. Had the first nine failures prevented Murray and Merrill from performing their first successful renal transplant, the world would be a vastly different place.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Shayan H. Organ transplantation: from myth to reality. J Invest Surg 2001;14:135-8.
2. Sayegh MH, Carpenter CB. Transplantation 50 years later--progress, challenges, and promises. N Engl J Med 2004;351:2761-6.
3. Merrill JP, Murray JE, Harrison JH, et al. Successful homotransplantation of the human kidney between identical twins. J Am Med Assoc 1956;160:277-82.
4. Murray JE, Merrill JP, Dammin GJ, et al. Study on transplantation immunity after total body irradiation: clinical and experimental investigation. Surgery 1960;48:272-84.
5. Calne RY. The rejection of renal homografts. Inhibition in dogs by 6-mercaptopurine. Lancet 1960;1:417-8.
6. Murray JE, Merrill JP, Dammin GJ, et al. Kidney transplantation in modified recipients. Ann Surg 1962;156:337-55.
7. Murray JE, Merrill JP, Harrison JH, et al. Prolonged survival of human-kidney homografts by immunosuppressive drug therapy. N Engl J Med 1963;268:1315-23.
8. Starzl TE, Groth CG, Brettschneider L, et al. Extended survival in 3 cases of orthotopic homotransplantation of the human liver. Surgery 1968;63:549-63.
9. Linden PK. History of solid organ transplantation and organ donation. Crit Care Clin 2009;25:165-84, ix.
10. Starzl TE, Eliasziw M, Gjertson D, et al. HLA and cross-reactive antigen group matching for cadaver kidney allocation. Transplantation 1997;64:983-91.
11. Organ procurement and transplantation network polices. Updated 2016.
12. Hardy JD. High ureteral injuries. Management by autotransplantation of the kidney. JAMA 1963;184:97-101.
13. Novick AC, Jackson CL, Straffon RA. The role of renal autotransplantation in complex urological reconstruction. J Urol 1990;143:452-7.
14. El Harrech Y, Abaka N, Ghoundale O, et al. Genital self-amputation or the Klingsor syndrome: Successful non-microsurgical penile replantation. Urol Ann 2013;5:305-8.
15. Fuller A, Bolt J, Carney B. Successful microsurgical penile replantation after a workplace injury. Urol Int 2007;78:10-2.
16. Bhanganada K, Chayavatana T, Pongnumkul C, et al. Surgical management of an epidemic of penile amputations in Siam. Am J Surg 1983;146:376-82.
17. Crowley IP, Kesner KM. Ritual circumcision (Umkhwetha) amongst the Xhosa of the Ciskei. Br J Urol 1990;66:318-21.
18. Nnamani NS, Janak JC, Hudak SJ, et al. Genitourinary injuries and extremity amputation in operations enduring and iraqi freedom: early findings from the trauma outcomes and urogenital health (tough) project. J Trauma Acute Care Surg 2016;81:S95-S99.
19. Ehrich WS. Two unusual penile injuries. J Urol 1929;21:239-41.
20. Tamai S, Nakamura Y, Motomiya Y. Microsurgical replantation of a completely amputated penis and scrotum: case report. Plast Reconstr Surg 1977;60:287-91.
21. Landström JT, Schuyler RW, Macris GP. Microsurgical penile replantation facilitated by postoperative HBO treatment. Microsurgery 2004;24:49-55.
22. Ishida O, Ikuta Y, Shirane T, et al. Penile replantation after self-inflicted complete amputation: case report. J Reconstr Microsurg 1996;12:23-6.
23. Koga H, Yamataka A, Wang K, et al. Experimental allogenic penile transplantation. J Pediatr Surg 2003;38:1802-5.
24. Zhao Y, Hu W, Zhang L, et al. Penis Allotransplantation in Beagle Dog. Biomed Res Int 2016;2016:1489204.
25. Hu W, Lu J, Zhang L, et al. A preliminary report of penile transplantation. Eur Urol 2006;50:851-3.
26. Zhang LC, Zhao YB, Hu WL. Ethical issues in penile transplantation. Asian J Androl 2010;12:795-800.
27. Bateman C. World's first successful penis transplant at Tygerberg Hospital. S Afr Med J 2015;105:251-2.
28. Dotinga R. Penile transplant: procedure raises technical, ethical issues. Urology Times 2016;44:28-34.
29. Halpern SD, Shaked A, Hasz RD, et al. Informing

candidates for solid-organ transplantation about donor risk factors. N Engl J Med 2008;358:2832-7.
30. Fischer S, Lian CG, Kueckelhaus M, et al. Acute rejection in vascularized composite allotransplantation. Curr Opin Organ Transplant 2014;19:531-44.
31. Kanitakis J, Petruzzo P, Badet L, et al. Chronic Rejection in Human Vascularized Composite Allotransplantation (Hand and Face Recipients): An Update. Transplantation 2016;100:2053-61.
32. Monstrey S, Hoebeke P, Selvaggi G, et al. Penile reconstruction: is the radial forearm flap really the standard technique? Plast Reconstr Surg 2009;124:510-8.
33. Hariharan S. Evaluation of candidates with a history of cancer. ASTS 3rd Annual Winter Symposium. 2003.
34. Parent B. Survey: Informing donors about hand and face transplants at NYU Langone Medical Center. 2014.
35. Sarwer DB, Ritter S, Reiser K, et al. Attitudes toward vascularized composite allotransplantation of the hands and face in an urban population. Vasc Composite Allotrans 2014;1:22-30.
36. United States Conference of Catholic Bishops. Ethical and religious directives for Catholic health care services. Origins 2001;31:153, 155-63.
37. al-Mousawi M, Hamed T, al-Matouk H. Views of Muslim scholars on organ donation and brain death. Transplant Proc 1997;29:3217.
38. Sellami MM. Islamic position on organ donation and transplantation. Transplant Proc 1993;25:2307-9.
39. Gillman J. Religious perspectives on organ donation. Crit Care Nurs Q 1999;22:19-29.
40. Siemionow MZ, Rampazzo A, Gharb BB. Addressing religious and cultural differences in views on transplantation, including composite tissue allotransplantation. Ann Plast Surg 2011;66:410-5.
41. Keown D. Buddihism, brain death and organ transplantation. J Buddh Ethics 2010;17:1.
42. Ikels C. Ethical issues in organ procurement in Chinese societies. China J 1997;No. 38:95-119.

Cite this article as: Rasper AM, Terlecki RP. Ushering in the era of penile transplantation. Transl Androl Urol 2017;6(2):216-221. doi: 10.21037/tau.2016.11.02

