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Mini-Review

Ethical issues in penile transplantation

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Abstract

This article provides an overview of the ethical issues associated with penile transplantation, a form of composite tissue allografting. There is only one reported case of human penile transplantation, and, as such, this technique is considered to be experimental. The ethical issues at stake involve both the graft donor and the graft recipient. With regard to the recipient, there are significant concerns relating to surgical risks and benefits, informed consent, body image (including surgical expectations and outcomes) and compliance. Donor issues may include family consent and privacy, as well as graft harvesting (leaving the donor cadaver without a penis). Many of these ethical issues can be explored during the recipient's assessment and consent process. Because no medium-term or long-term outcome data for this procedure exist—only one such operation has ever been performed—the burdens and ethical issues concerning penile transplantation remain unknown.

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1 Introduction

Penile defects are uncommon, yet challenging conditions that are often associated with severe physiological and psychological problems. Usually, the patient is unable to void in a standing position and has difficulty during intercourse, in which case both the patient and his partner are likely to strongly desire correction of the defect. There are currently four options for treatment: penile replantation, penile reconstruction, penile lengthening and penile transplantation. Penile reconstruction is now a major method of treating penile defects worldwide. In 2003, Koga reported on the results of experimental allogenic penile transplantation using experimental animals [1]. Penile transplantation, on the other hand, is still in its experimental phase. This procedure, which is a form of composite tissue allografting, has only been performed once in China to date [2, 3]. The Guangzhou General Hospital of Guangzhou Military Command does, however, have a protocol for such a procedure. The hospital's Institutional Review Board has approved penile transplantation, and an evaluation of potential research subjects is underway.

2 History of human composite tissue allografting

Composite tissue allografting involves the concurrent transplantation of multiple structures. The first known instance of composite tissue allografting in humans appears to have been a leg transplant from a deceased Ethiopian Moor to a Roman priest who had a cancerous leg, circa 348 AD [3]. The first human hand transplant was attempted in 1964 in Ecuador, but, due to rejection, it required removal after only 2 weeks [4]. The first successful human hand transplant occurred 34 years later [5], as did the first successful human larynx transplant [6]. Other milestones include lower limb and

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hindquarter transplantation [7], as well as transplantation of the abdominal wall [8], tongue [9], uterus [10] and testis [11]. Partial human face transplants have also been performed, with one reported in France [12] and one in China [13].

Of all the different known forms of composite tissue allografting, penile transplantation seems most ethically similar to facial transplantation. Dubernard *et al*. [12] performed the first human partial face allograft on 27 November 2005. They reported on the postoperative outcomes of that procedure in 2007, 18 months after the fact, in an article published in *The New England Journal of Medicine*.

3 Why perform penile transplantation?

The question of why penile transplantation should be performed is important and has a complex answer. First, penis defects that result from trauma can be functionally devastating. In such cases, the tissues of the corpus cavernosum penis, urethra, glans penis and/or penile skin may be severely and permanently damaged. Currently, there are four treatment options in this scenario: penile replantation, penile reconstruction, penile lengthening and penile transplantation. Penile reconstruction using microsurgical techniques is feasible and can result in the preservation of sensation and sexual function [14, 15]; however, this method has a number of shortcomings, such as the need for multiple operations and its often unsatisfactory cosmetic outcomes [16]. Penile lengthening also has limitations, as lengthening the penis may induce nerve and/or vascular damage. Penile replantation requires limited ischemic time and the distal amputated penis [2]. Although penile transplantation is a comparatively new and untested procedure, the first human face allograft [17] provides evidence of successful experiences and gives us confidence in the procedure's potential.

Second, traditional Chinese ways of thinking consider the penis to be the ''life-spring'' essential to carrying on the ancestral line. Indeed, they regard it as the symbol of manhood. Therefore, to varying extents, many Chinese people value the penis's symbolic meaning even more than its physiological function. When penile deformation occurs, not only does the patient experience personal psychological trauma, but those around the patient who hold these traditional beliefs can exacerbate the problem. Even if the patient can adjust and accept his appearance, some people in society do not, and the patient may be subject to ridicule and cruel comments. In a society that values 'normalcy' and rejects 'abnormality,' having a penile defect is not an insignificant matter.

This collateral emotional damage that can result from suffering a penile defect can be substantial. Patients were commonly 'extremely concerned' about how their defect would affect their status in their family and in society [18]. They also worried that their wives would abandon them and often suspected their wives of having extramarital affairs. In light of the facts presented, exploring ways to improve the penis's appearance and functional challenges in individuals with severe penile defects is a worthy goal.

4 Ethical considerations

Very little has been published regarding penile transplantation. Several organizations hailing from both the medical field and the general public have expressed serious concerns about penile transplant procedures. In China, a search using the Google internet search engine returned 219 000 comments related to penile transplantation. Many people have urged that several aspects of this novel therapeutic approach need to be considered. Mainly, they argue that the benefits of the procedure should be weighed against its associated disadvantages. However, the fact that performing such an innovative and controversial procedure represents a forward step for contemporary medicine raises further issues of its own. When dealing with this novel therapeutic approach, various aspects need to be considered, mainly the benefit obtained versus the associated disadvantages. Unfortunately, the procedure's newness means that there has been insufficient consideration of many of the important ethical issues relating to the use of modern therapeutic techniques for treating borderline medical conditions. These medical approaches may be affected by the changing definitions of such social and cultural aspects of human life as sexuality, gender and aging.

The Guangzhou General Hospital of the Guangzhou Military Command of China prepared a working party report on penile transplantation in 2006. At that time, the hospital reviewed the surgical, immunological, psychological, societal, ethical and legal aspects of the procedure. Although the report took into account the suffering of patients with severe damage to the penis, it argued that the current state of research knowledge

did not justify allowing human penile allografting to occur. The hospital professed that it was not averse to the concept of penile transplantation but, rather, that the timing was not suitable due to unresolved concerns about immunosuppression (regimen and risks), psychological impacts on the graft recipient and the donor family and how to obtain valid informed consent.

After the first penile transplant, the Guangzhou General Hospital of Guangzhou Military Command released a joint statement outlining the psychological issues related to penile transplantation and a list of 10 principles to guide surgeons in deciding whether to perform the procedure. These guidelines recommended that the procedure be restricted to individuals with severe injuries who are unwilling to undergo traditional reconstructive surgery. The guidelines also stated that the results of each procedure must undergo peer review and that all research subjects should be informed of any early results that are 'less than optimal', as this eventuality could affect future clinical management decisions and clinical outcomes.

5 Guiding principles for penile transplantation

(1) Penile transplantation should be performed only in patients with severe damage to the penis.

(2) Penile transplantation should be done in appropriate institutions under the protocols approved by institutional review boards.

(3) Institutions should have surgical and transplantation expertise, and transplantation teams should include multidisciplinary experts such as plastic surgeons, immunology/transplant specialists, infectious disease and oncology specialists, medicolegal experts, physical therapists, pharmacology specialists, patient advocates and media relations representatives.

(4) Appropriate selection criteria should be established, and the risk/benefit ratio must be considered for each individual patient.

(5) Patients and their families should be presented with special informed consent documents explaining the risks, benefits, alternatives and innovative nature of the procedure.

(6) Candidates for penile transplantation should undergo a thorough psychiatric and psychological evaluation, including evaluation of their psychosocial support system.

(7) Patients with known psychological and psychiatric diagnoses, poor coping skills, poor support systems or a history of noncompliance are poor candidates for penile transplantation.

(8) Due to the novelty of the procedure, proceeding in incremental steps and gathering more evidence from research done in the field are necessary to ensure its appropriate application.

(9) Peer review of the penile transplantation procedure is mandatory to ensure compliance with medical standards of care and objective assessments of the outcomes.

(10) The ethics of performing a new procedure with unknown outcomes must be carefully assessed and weighed against potential benefits to the selected group of patients with severe penile damage following the evaluation of such candidates for penile transplantation by medical ethics specialists.

On the basis of the hospital's regulations, the 10 guiding principles mentioned above must be implemented before allogenic penile transplantation. We think they are necessary and fundamental guiding principles, although the procedure, which is still in its trial period, may present unpredicted challenges as well. Therefore, approvals for such surgery should be strictly constrained, avoiding causing more severe physical and emotional injuries to the patients and preventing the occurrence of serious mental diseases.

6 Informed consent

The ethical issues involved in penile transplantation cross many disciplines, including regulatory affairs, immunology and psychology. Most prominently, the informed consent process has been (appropriately) placed under the microscope due to its ethical complexity [19, 20]. Presenting patients with adequate and appropriate information is critical to the informed consent process; however, in the case of penile transplantation, the volume of information available to potential research subjects is limited, as the procedure has been performed only once in humans. In addition, the information about penile transplantation is complex, involving many types of anatomic structures, multiple reconstructive techniques and complicated pharmacological treatments. The absence of coercion is critical to ethical treatment, and research teams should take all possible steps to avoid, minimize and disclose their conflicts of interest [19, 20]. Particularly in the case of experimental techniques such as this one, it is easy to see how eager surgical teams and desperate patients

could become inappropriate partners in a relationship in which the patient becomes a research subject first and a patient second.

Thus, since penile transplantation is a highly complex area of clinical research, the use of a research subject advocate in the consent process is warranted. The advocate (often a bioethicist) is not part of the research team, yet understands the ethical and scientific issues associated with the study. Further, the advocate ensures that patients have the functional capacity to consent to participate in the study and educates them with regard to the risks, potential benefits and alternatives to treatment, as well as about the experimental nature of the study, in an attempt to eliminate any patient misconceptions. The advocate also ensures that potential subjects understand that there may be risks that are currently unknown to the research team. During this process, the advocate attempts to elucidate the motivations of the patient and to identify if he or she is under any coercion to participate, all with the aim of protecting the welfare of the research subjects.

7 Immunosuppression

The ethical concerns surrounding immunosuppression require researchers to consider the potential benefits of penile transplantation in light of the burdens and risks of its accompanying drug regimens, as skin is one of the most antigenic tissues in the body [19, 21]. Generally speaking, immunosuppression regimens for composite tissue allografting protocols are similar to those used in kidney transplantation. The standard induction drugs are typically steroids, anti-thymocyte globulins and anti-CD3 monoclonal antibodies. Maintenance therapy after the transplant usually includes prednisone, tacrolimus and mycophenolate mofetil. Each of these drugs has its own unique side effect profile; however, the universal concern with these drugs is their potential to predispose a patient to opportunistic infections, end-organ damage, diabetes and lymphoma [21–23]. Following a lifelong regimen of immunosuppressive, anti-rejection drugs is an acceptable trade-off in the case of life-maintaining organs such as the heart, kidneys or liver. The penis is not a life-maintaining organ, but it should not be considered a general organ either.

8 Psychosocial issues

As mentioned earlier, the emotional and psychological burdens of living with a penis defect can be substantial. Even so, research subjects must demonstrate that they understand that, due to the experimental nature of penis transplantation, there is a risk of allograft failure and rejection. Subjects must also accept that there is potential for the procedure to result in decreased penile function and performance, as well a less desirable visual appearance. Failed penile transplantation is likely to be accompanied by devastating psychological effects similar to those seen in cases of failed penis replantation. In situations of graft failure or insurmountable rejection, the graft would have to be removed and replaced with the transplant recipient's own tissue (autograft). During the consent process, these risks must be emphasized to all potential research subjects. Individuals who are already emotionally or psychologically impaired may not be able to tolerate these potential outcomes and should not be considered appropriate candidates for penis transplantation. That is to say, each potential subject should be individually assessed by a clinical psychiatrist regarding their psychiatric history and coping skills [24, 25]. At this juncture, a social worker should explore the patient's social support system, access to health care and general psychosocial stability.

Subjects need to be able to confront their transplant as well as integrate it into their lives (that is, accept it as their own). The transplant literature tells of numerous cases in which graft recipients have had significant adjustment problems after transplantation. Some transplant recipients are psychologically unable to accept the graft as part of their own body or worry excessively about the graft donor [26, 27]. In one case, when the recipient found out who the donor was, he became very upset and committed suicide [28]. As it is more complex than other types of organ transplantation, penis transplantation will require the recipient both to comply with the immunosuppressive regimen and to participate in a multifaceted rehabilitation program (for example, physiotherapy, speech therapy) to facilitate the repair of sensory and erectile function. Further, the psychological needs of the patient's partner deserve high attention during both the pre- and the postoperative periods. It is important that the patient's partner should appropriate the graft, which may sometimes be more important than the patient's own acceptance of it. Research subjects who experience significant body image or identity problems after the transplant and resist rehabilitation may be at a higher risk of experiencing problems with graft

function. Regarding this point, human penile transplantation should learn from the postoperative practices established for cases of partial face transplantation. Specifically, psychological support should be provided once daily during the first 4 postoperative weeks, twice weekly for the next 4 months, and, thereafter, once a month or at the request of the patient or his wife [12].

9 Donor issues

Several ethical issues pertain to the graft donor [29]. Before their death, not all individuals will have declared their stance on organ and tissue donation, and even fewer will have thought about the possibility of donating their penises. For families grieving the death of their loved one, discussing the concept of harvesting the tissues of the penis could be frightening or even 'off limits' due to emotional stress. In theory, individuals who expressed a wish to be organ or tissue donors might have been more inclined to be penile graft donors, compared with those who never expressed any donation wishes; however, we could test this theory only by surveying individuals using a hypothetical scenario; to date, this research has not been done. As such, the family's consent must be obtained in a sensitive and compassionate manner, and the family should be fully informed about the nature of the research study, the nature of the harvesting process, potential privacy issues and the resultant inability to have an open-casket funeral.

An occasional transsexual patient undergoing a surgical sex change might be able to serve as a living penis donor. However, the viability of using a living-donor penis from a transsexual patient is highly debatable. Technically, the penile skin would be used for reconstruction of the vagina during the male to female transsexual surgery. The denuded penis is obviously not suitable for transplantation. More complex surgical design has to be developed, either to find substitute tissues to cover the reconstructed vagina in the donor, or to use other skin grafts to cover the denuded penis for the recipient. Additionally, the acceptability of this surgery, to both the penile donor and the recipient, as well as their families, could present a tricky psychological challenge. The availability of penises from transsexual donors could also be problematic compared with those from brain dead donors. If a living-donor penis were to be used, privacy protection would be crucial, and the consequences of improperly released information could be catastrophic.

The donor's personal information should not be revealed to the recipient. Conversely, the donor's family should not be given personal information about the recipient by the research team or the tissue procurement organization. This latter situation is, however, confounded by the fact that the research team will likely wish to publish its research results. Although, in this scenario, the donor's identity would be masked somewhat, it is likely that such information could be inferred by the donor family. In addition, the recipient might potentially make media appearances or speak at transplant conferences, thereby publically broadcasting his identity. In short, the confidentiality and privacy safeguards are equally important for both the graft donor (and his family members) and the graft recipient (and his family members).

10 Conclusions

In this review, several ethical issues associated with penile transplantation are identified. We think that these issues are not insurmountable and that it is ethically appropriate to pursue this human research application. Nonetheless, we admit that, as only one procedure of this kind has been performed and no medium-term or long-term outcome data are available, the precise burdens and ethical problems related to penile transplantation remain unknown.

Competing interests

The authors declare that they have no competing interests.

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