Ethical considerations during a pioneering surgical procedure: porcine cardiac xenotransplantation

Abstract

Preclinical advances in life-sustaining porcine cardiac xenotransplantation from donor pigs to baboons have paved the way for the performance of porcine cardiac xenotransplantation in a human. This procedure was performed with emergency use authorisation granted by the United States Food and Drug Administration under the umbrella of investigational new drug use on compassionate grounds. The patient was denied candidacy for durable mechanical circulatory support and heart transplantation as a result of non-adherence to medical advice.

Successful porcine cardiac xenotransplantation in humans will significantly increase the availability of potential donor organs for long-term management of end-stage heart failure. Human porcine cardiac xenotransplantation is associated with ethical conflicts encompassing multiple ethical principles which are not mutually exclusive and are sometimes conflicting. This article focuses on some of the ethical conflicts encountered in relation to the use of mechanical circulatory support, pretransplant evaluation, shared decision making during informed consent, infectious disease risk, preclinical and clinical testing, and the role of regulatory bodies during performance of the first human porcine cardiac xenotransplantation.

An increase in human trials of xenotransplantation procedures is imminent. Potential ethical conflicts associated with xenotransplantation should be addressed appropriately.

Key words: Cardiac xenotransplantation; Extracorporeal membrane oxygenation; Heart transplantation; Non-adherence to medical advice; Xenogeneic infections

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Introduction

The goal of surgical innovation is improved clinical outcomes and patient satisfaction, but scientific innovation does not automatically come with ethical balance, and considerations are complex. Xenotransplantation is the process of grafting or transplanting organs or tissues between members of different species. Preclinical advances in non-human primates have resulted in the performance of xenotransplantation in human patients, raising complex ethical challenges and reinvigorating the ethical debate surrounding xenotransplantation. Porrett et al (2022) reported a renal xenotransplant in a brain-dead recipient. A life-sustaining orthotopic porcine cardiac xenotransplant was recently performed at the University of Maryland. More clinical xenotransplant trials are on the horizon and the ethical considerations are significant. Future conflicts may arise because of patient preference, lack of evidence for successful use in humans, potential for complications and infections, animal rights concerns, or differences in social norms and religious beliefs. This article explores some of the ethical and moral challenges surrounding the performance of human porcine cardiac xenotransplantation.

Ethics and clinical practice

Four important principles in medical ethics are autonomy, non-maleficence, beneficence and justice. Autonomy refers to the right of a patient to determine what is done to their body. Non-maleficence is the obligation of the clinician not to harm the patient. The prescribed therapy should be beneficial to the wellbeing of the patient under the principle of beneficence, while justice refers to fairness in the distribution of healthcare resources.

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Other ethical principles include the requirement for informed consent, truth-telling, confidentiality, defining goals of care, decisional regret and futility. These principles are not mutually exclusive and are sometimes conflicting. Varkey (2021) proposed a four-step practical approach to resolving ethical conflicts.

1. Clinical assessment to identify medical problems, treatment options and goals of care
2. Finding and clarifying patient preferences on treatment options and goals of care
3. Defining effects of medical problems, interventions and treatment on quality of life
4. Identifying family, cultural, spiritual, religious, economic and legal factors that give rise to ethical conflicts.

This model may be used to navigate and solve ethical conflicts when making clinical decisions, with an option to seek expert opinion or perform literature searches when necessary. Ethical decisions regarding experimental treatments, end-of-life care and withdrawal of life-supporting equipment are especially challenging.

Professionalism

Healthcare teams are required to maintain a high level of professionalism when interacting with patients. This enhances public trust. Two major components of professionalism are ethics and morals. Surgeon-led healthcare teams have a moral duty to work within the limits of their technical skills while performing procedures that are beneficial to patients and society at large. Cardenas (2020) stated that 'a proficient surgeon is considered to be not only competent to perform the art and science of surgery as traditionally understood, but also to be ethically and morally reliable.' Performance of innovative procedures should be accompanied by heightened levels of professionalism and proficiency in the healthcare team, with management goals of improved patient comprehension and outcomes.

Clinical scenario

A 57-year-old patient ('patient X') presented with cardiogenic shock and refractory ventricular tachycardia secondary to ischaemic cardiomyopathy. Veno-arterial extracorporeal membrane oxygenation was emergently initiated as a bridge to decision. Two months later, he remained bedridden on veno-arterial extracorporeal membrane oxygenation and had become deconditioned with sarcopenia and skin changes in his lower extremities. He was alert, oriented and cognitively intact, and did not require mechanical ventilation. He was denied candidacy for durable mechanical circulatory support such as a left ventricular assist device and heart transplantation by a multidisciplinary heart failure management team because of persistent non-adherence with medical advice during earlier heart failure management.

The patient was offered porcine cardiac xenotransplantation with the hope that emergency use authorisation or compassionate use would be approved by the United States Food and Drug Administration and the institutional review board as a lifesaving procedure under the umbrella of investigational new drug use. The medical centre also agreed to fund the procedure since insurance coverage was not available for porcine cardiac xenotransplantation. Conflicts related to the four key ethical principles were thus raised. Was the patient competent to authorise the performance of porcine cardiac xenotransplantation on himself (autonomy)? Was this the best option for him? What would be his quality of life after porcine cardiac xenotransplantation (beneficence/non-maleficence)? Should an experimental transplant procedure be performed in a patient who has demonstrated non-adherence to medical advice? Would he be adherent to medical advice after xenotransplantation, and should the medical centre agree to fund the procedure (justice)? These and other ethical questions were considered by the family, medical team and medical centre before this proposed procedure.

Mechanical circulatory support

Crespo-Leiro et al (2018) and Hayanga et al (2020) reported on progress with use of mechanical circulatory support devices that has led to improved outcomes in the management of patients with end-stage heart and lung diseases respectively. These include extracorporeal membrane oxygenation, ventricular assist devices and total artificial hearts, and they have been

used as a therapeutic bridge to decision, recovery, implantation of a more durable mechanical circulatory support device or transplant. Ethical questions related to their use arise before initiation, during management and in relation to decisions about discontinuation of therapy, with the latter the most controversial in the context of withdrawal of life support systems.

Sonntag et al (2019) have advocated for the education of resident and fellow physicians on the ethics of mechanical circulatory support when considering patient beneficence, respect for autonomy, informed consent, shared decision making, surrogate decision making and end-of-life care. Enumah et al (2021) suggested that the use of guidelines for extracorporeal membrane oxygenation candidacy that have been vetted by a multidisciplinary group may help to avoid its inappropriate use and patient harm. Patient X was placed on veno-arterial extracorporeal membrane oxygenation emergently to preserve life and as a bridge to decision. The hope was that he would either recover and be weaned off this or progress to a more durable cardiac failure management strategy, but he remained on extracorporeal membrane oxygenation for 2 months with multiple failed trials of weaning. This was primarily because he had cardiac arrhythmias that were not improved by multiple medical and procedural interventions.

Patient X's candidacy for durable mechanical circulatory support or heart transplantation was evaluated by a multidisciplinary heart failure management team. The team determined that he was not a suitable candidate because of his previous persistent non-adherence to medical advice. He was independently evaluated by two other high-volume heart transplant programmes, and both arrived at the same conclusion. Therefore, patient X had no strategy available to take him off extracorporeal membrane oxygenation. In a review of 235 patients treated with extracorporeal membrane oxygenation at the Mayo Clinic in Rochester, Minnesota, DeMartino et al (2019) reported that withdrawal of extracorporeal membrane oxygenation was requested in 26% of unrecovered patients. None of these patients had decision-making capacity and 82% had extracorporeal membrane oxygenation initiated as a bridge to decision, 13% to transplant and 5% to mechanical circulatory support. Patient X was unique in that he had decision-making capacity and was not on any other life support device such as a mechanical ventilator or renal replacement therapy.

Pretransplant evaluation of transplant candidates

In a retrospective review of 60 ethics consultations performed in solid organ transplant candidates and recipients in a large academic medical centre, Courtwright et al (2021) reported that three out of thirty-nine candidates were denied transplantation as a result of non-adherence to medical requirements such as cessation of alcohol use, consistent outpatient follow-up and adherence to medication management. Ethics consultations were performed more frequently among heart and lung transplants than in kidney and liver transplants. Sandal et al (2021) reported that non-adherence to medical requirements is recognised by several major transplant societies as a relative or absolute contraindication to organ transplantation because it is associated with elevated risk for post-transplant non-adherence. Heart transplantation is limited by the availability of suitable donors with many candidates on transplantation wait lists. Therefore, strict suitability criteria are used to identify patients with the greatest need and who are also likely to maximise the clinical benefits and outcomes from transplantation. Patient X's history of non-compliance was weighed against his current situation, mental state and willingness to do whatever was medically necessary for his survival. According to Sandal et al (2021), there may be a risk of bias during psychosocial evaluation for risk of non-adherence that may cause inequity in access to transplantation. Although disputed, a 6-month observation period for demonstration of adherence in transplant candidates may be accepted by various organisations. However, a 6-month delay to assess adherence to medical requirements was not a viable option in patient X.

Informed consent

Approaches to informed consent have changed over the years from the paternalistic model ('doctor knows best') through the informative model (give patients information and let them choose) to the more recent interpretive or shared decision-making model. Cocanour (2017) suggested that the latter focuses more on explaining a realistic range of best and

worst outcomes for the patient's clinical diagnosis and treatment while guiding the patient, their family and physician to make an informed decision about goals and expectations for treatment based on the patient's preferences and values. The patient must also be competent, adequately informed and not coerced. According to Paredes (2020), during shared decision making, the patient's opinion and choice form the cornerstone for management decision making. The surgeon has a moral duty to treat the patient but is not under any ethical obligation to perform medically unnecessary or futile procedures.

Cocanour (2017) stated that informed consent is not necessary during a public health emergency, a medical emergency, when the patient requests not to be informed or is incompetent, and when the physician feels that disclosing information to the patient will harm the patient. Patient X was evaluated by four independent psychiatrists to ascertain his cognitive competence in consenting to xenotransplantation. He knew the procedure had never been performed in humans and that it was an experimental procedure for which the outcome was unknown. All potential perioperative risks were explained to him, including the potential for temporarily remaining on extracorporeal membrane oxygenation after porcine cardiac xenotransplantation with the possibility of converting to human cardiac transplant after demonstrated compliance with medical advice. He also knew that the only other options available to him were either to stay on extracorporeal membrane oxygenation indefinitely or discontinue it. The decision to proceed with porcine cardiac xenotransplantation was a shared decision between patient X, his family and his care team.

Infection risk

The risk of infection transmission to the patient, healthcare workers or the community after xenotransplantation is significant but not well defined. Measures that reduce the risk of transmission include breeding pathogen-free animals in a sterile facility, early weaning of the animals, and screening of animals for pathogens including but not limited to porcine adenovirus, porcine influenza virus, porcine cytomegalovirus, porcine gamma herpesvirus, porcine circovirus and porcine endogenous retrovirus. According to Brenner and Mihalj (2020), because porcine endogenous retrovirus may be integrated in the porcine genome, selective breeding and genetic modification may be used to reduce the risk of transmission. Sade and Mukherjee (2022) suggested that lifelong clinical and laboratory surveillance of xenotransplant recipients and close contacts for xenogeneic diseases can mitigate public health risk for outbreaks and that maintenance of a registry of xenotransplant patients may facilitate detection of subtle outbreaks. There is also a risk for infection transmission to patients exposed to surgical instruments and other devices used in treatment of patients undergoing xenotransplantation. Efforts to reduce risk of transmission were enacted. Patient X was managed in a private room and contact with staff was limited. Surgical instruments used in his care were quarantined, cleaned with bleach solution and reserved for use only in potential subsequent xenotransplantation procedures. Every effort was made to use disposable equipment. The operating room was extensively cleaned with bleach after care of patient X. When possible, reusable equipment such as the echocardiography probe was used with a protective cover. Measures were put in place to limit healthcare workers' contact with the patient, laboratory specimens and equipment used in the care of the patient. Healthcare personnel were also given the option to decline participating in the care of the patient.

Preclinical testing

Innovative ideas, methods or devices are usually introduced to clinical practice to improve outcome measures such as survival, complication rates, pain control, recovery rates, quality of life, cost and patient satisfaction. Innovative clinicians who perform novel surgical procedures may be perceived to push boundaries for advancement of science and technology, discovery of better methods of treatment and a desire to treat people with no other recourse for therapy. Less noble, unethical goals include enrichment, achievement of fame or attempts to break a record.

In general, preclinical evaluations and testing of innovative procedures are completed before their introduction to clinical practice. However, this process is highly variable, and sometimes human volunteers or laboratory animals are used. Regulatory bodies evaluate preclinical

data from the novel procedures to confirm efficacy and ensure safety standards are met. For emergent or lifesaving procedures, it may be impossible to satisfy all the prerequisite regulatory requirements. The ethical questions that must be addressed in relation to the initial performance of an imminently lifesaving novel surgical procedure are complex and vary significantly among individual clinical circumstances. According to the report of the Xenotransplantation Advisory Committee of the International Society for Heart and Lung Transplantation by Cooper et al (2000), 'a clinical trial should be considered when approximately 60% survival of life-supporting pig organs in non-human primates has been achieved for a minimum of 3 months, with at least 10 animals surviving for this minimum period. Furthermore, evidence should suggest that longer survival (>6 months) can be achieved'. Mohiuddin et al (2022) have reported consistent survival beyond 6 months in non-human primates after orthotopic porcine cardiac xenotransplantation with survival for almost 9 months in one case and survival for up to 945 days of heterotopic porcine cardiac xenotransplantation in non-human primates.

According to Cowan and Tector (2017), prolonged survival in preclinical models of cardiac and renal xenotransplants, in combination with advances in gene editing technology and reduced risk of transmission of infections such as porcine endogenous retrovirus, have led to an upsurge in interest in xenotransplantation. These advances paved the way to human clinical testing of xenotransplantation.

Clinical testing

Randomised controlled trials are used for rigorous comparison of clinical outcomes from two different clinical interventions. The ethical conduct of a trial requires that the patient be informed that they are participating in an experimental procedure while counselling them about other available therapeutic options. The researcher should be convinced that outcomes after the novel intervention are comparable to standard therapy. Double blinding of the investigator and recipient of therapy is used to minimise bias, but this is not always possible with surgical trials. Robinson et al (2021) observed that randomised controlled trials designed to validate surgical innovation are small and associated with a significant risk of bias, poor control for experience of surgeon, and poor assessment of the quality of the intervention. However, Savulescu et al (2016) argue that randomised controlled trials are necessary and can be performed with a placebo procedure when certain conditions are met. According to Cowan and Tector (2017), the pace of progress in several areas of xenotransplantation suggests that clinical trials may no longer be a distant prospect.

Following favourable results from porcine cardiac xenotransplantation in non-human primates, regulatory approval from the Food and Drug Administration and the institutional review board had already been granted to perform a 48-hour trial of life-sustaining orthotopic porcine cardiac xenotransplantation in a brain-dead patient, but a suitable recipient had not been identified at the University of Maryland. The Food and Drug Administration (2016) in its guidance document for the use of xenotransplantation recommends this in 'patients with serious or life-threatening diseases for whom adequately safe and effective alternative therapies are not available'. Brenner and Mihalj (2020) thought that strict medical and ethical guidelines and regulations would be needed before first clinical use of xenotransplantation because of the risk of zoonotic infections and immunosuppressive regimens that have not been tested in humans.

Patient X did not qualify to be on the heart transplant list despite his reliance on veno-arterial extracorporeal membrane oxygenation for survival. Performing a life-supporting orthotopic porcine cardiac xenotransplantation appeared to be the only option for his survival. Performing randomised controlled trials in porcine cardiac xenotransplantations may become a viable option after these have been proven to be a consistent and reliable management option for end stage heart failure under certain clinical conditions similar to those of patient X.

Regulatory bodies in surgical innovation

Medical regulatory agencies that enforce safety standards to protect the public from unethical practices and dangerous exposures include the Food and Drug Administration (2022a, 2022b) and the Medicines and Healthcare Products Regulatory Agency in the UK. The Food and Drug Administration (2022b), under the umbrella of emergency use authorisation, can:

Key points

- Clinical introduction of human xenotransplantation is associated with ethical conflicts.
- Patients may be denied candidacy for heart transplantation as a result of non-adherence to medical advice.
- There is a public health risk for xenogeneic infectious disease outbreaks associated with xenotransplantation.
- Preclinical milestones in non-human primate xenotransplantation models suggested by the advisory committee of the International Society for Heart and Lung Transplantation have been achieved.
- Ethical conflicts associated with human trials of xenotransplantation procedures should be addressed appropriately.

'authorise unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by chemical, biological, radiological, and nuclear threat agents when certain criteria are met, including there are no adequate, approved, and available alternatives.'

The institutional review board is a localised regulatory agency that ensures that the rights and wellbeing of individuals participating in research studies are upheld, and typically consists of scientific and non-scientific members. Hurst et al (2020) suggested in a commentary that because of the unprecedented ethical questions raised, institutional review board members should receive some form of education in xenotransplantation before the scheduling of xenotransplant procedures. The Food and Drug Administration and institutional review board granted permission for the porcine cardiac xenotransplantation to proceed in patient X.

Conclusions

The first human orthotopic porcine cardiac xenotransplantation has been performed in a patient with end-stage heart failure. This pioneering surgical procedure was associated with ethical conflicts. Subsequent trials of porcine cardiac xenotransplantation should be introduced cautiously. An increase in trials of xenotransplantation procedures should be anticipated. There are still challenges related to use of porcine cardiac xenotransplantation in humans: mechanisms of rejection and immunosuppressive regimens are not well understood, public health risk of infections should also be addressed, and ethical concerns remain. Current approval for use of porcine cardiac xenotransplantation is for a 48-hour trial in brain-dead individuals and is likely to remain in place until more clinical data about porcine cardiac xenotransplantation becomes available.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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