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The Phenomenon of Xenotransplantation in The Medical World in Terms of Potential, Risk, Ethics And Islamic Perspectives

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ABSTRACT

Transplantation is a process of transferring organs that are still functioning properly to replace organs that are no longer functioning. However, due to the limited number of organs for transplantation, interspecies transplants are performed, namely transplants between animals and humans called Xenotransplantation. Xenotransplantation is a technique of transplanting animal organs or tissues into human organs or tissues that can no longer function. Xenotransplantation can be one way to overcome the availability of transplant organs for humans. The most potential animal that can be used is the pig because it is almost similar to humans. However, xenotransplantation still causes problems due to immune rejection in the donor and the risk of transmission of infection. The purpose of writing this review article is to find out the potential, risks, and religious perspectives regarding xenotransplantation carried out in the health world. The method used in the preparation of this article is a literature study conducted by reviewing several journals, books and research articles related to xenotransplantation. To overcome the problems caused by xenotransplantation, genetic engineering is carried out in animals in order to produce more compatible organs. Thus, there are several successful organ xenotransplantation experiments although they still require further development. Ethically and legally, xenotransplantation is allowed as long as it is not abused and can save the patient. With the development of biotechnology, xenotransplantation is expected to be an alternative solution that can be used to overcome the scarcity of transplant organs in the future. So the use of xenotransplantation can potentially be an alternative solution that can be used to overcome the scarcity of transplant organs for humans. The risks resulting from the process can be reduced with further research to create animal organs that are suitable for the human body. In the perspective of Islam, xenotransplantation is allowed if it is done to save lives and not to abuse the animal.

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1. INTRODUCTION

Technological developments in various scientific fields continue to grow very quickly. Researchers continue to innovate to develop renewable technology every year. Including technology that can be used in the health sector to support a more sophisticated health system and has many benefits for the community (12). Discoveries that develop in the world of health can indirectly provide new hope and enthusiasm for people who have poor body condition. Decreased body condition can occur due to exposure to microorganisms that can cause damage to organs so that they cannot function.

One of the discoveries in the health sector that can be a solution for the organ to return to normal function is transplantation (20)

Transplantation is a process of transferring organs that are still functioning properly to replace organs that are no longer functioning. Organs that can be used as transplant material are the eyes, heart, and kidneys (10). The transplant process was first pioneered in 1873-1944 by a French biologist and surgeon named Alexis Carrel. In 1896 Carrel conducted a dog kidney transplant experiment which became the beginning of transplantation. One year later, an animal tissue transplant experiment was successfully carried out by John Murphy. In 1954, Dr. J. E. Murray successfully performed a kidney transplant between twins, so transplants continued to be used (30). But a new problem arose, namely the limited availability of transplant organs while the need was quite high. So the researchers innovated to perform transplants between species, namely between animals and humas, which is called Xenotransplantation (11).

Xenotransplantation is the process of transplanting animal organs or tissues to replace organs or tissues of the human body that are no longer functioning. Xenotransplantation can also be called heterotransplantation, which is a transplant in which the donor and donor are two different species. Because transplants are carried out from animal tissues or organs to other animals or from animals to humans (31). Xenotransplantation aims as an effort to help humans recover from diseases that occur due to damage to organ, tissue or cell function using donors from animals (31). The existence of xenotransplantation occurs because of the many needs and requests regarding organ transplants but the core donors. So xenotransplantation is used as a solution to these events (20).

The animals that can be used are goats, cows, monkeys, baboons and pigs. However, according to researchers, the most appropriate animal that can be used for transplantation into humans is the use of pigs as donors because some organs, especially the heart, are almost the same size as humans and pigs can be kept and easily raised under pig control (8). In addition, pigs contain a dangerous virus, *Porcine Endogenous Retrovirus* (PERV), which although inactive, is a concern if used as a donor animal because it can potentially transmit the virus to the recipient (22).

The use of xenotransplantation can cause problems for the human body because the human body will perform immunological rejection of the transplanted organs. In addition, the use of xenotransplantation can interfere with animal welfare because the animals used for transplantation will be kept like laboratory animals because they must be in sterile conditions to minimize pathogen infection so that the animals remain healthy so that the source of transplantation is safer. Although these conditions are much better than being kept on a farm, it can interfere with the biological and psychological properties of the animal (25). The purpose of writing this review article is to find out the potential, risks, and religious perspectives regarding xenotransplantation carried out in the world of health.

2. METHOD

The data collection method used in the preparation of journal reviews is literature study. This literature study was conducted by reviewing several journals, books and research articles related to xenotransplantation. Literature searches were conducted through google scholar with journals obtained in the 2014-2024 publication time range.

3. RESULT AND DISCUSSION

3.1 Definition of Xenotransplantation

Xenotransplantation is the use of living cells, tissues or organs that are transplanted between different species (29). Xenotransplantation is a term that describes the procedure of transferring organs or transplants from animals to humans (28). Xenotransplantation is a technique of transplanting animal organs or tissues into human organs or tissues that can no longer function. In general, the transplantation process is carried out based on genetic similarity, where humans have genetic similarities with primate animals (20). However, this process is also usually performed from other animals such as cows, goats, monkeys, baboons and pigs.

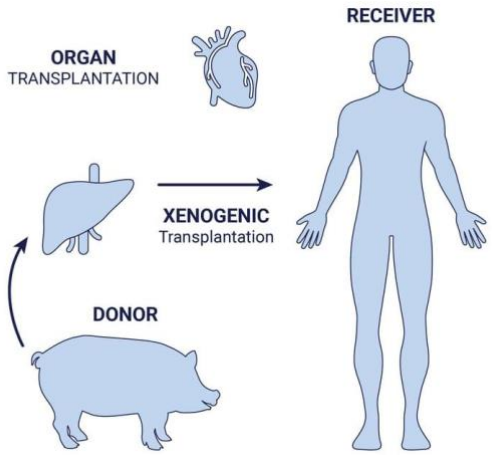

Figure 1. The general concept of xenotransplantation

Xenotransplantation has several advantages, including an almost unlimited source of organs, the transplant process can be carried out as soon as possible when needed, and organ transfer can be carried out as an alternative to complete healing or as an intermediate medium until a suitable organ is found (29, 20). On the other hand, xenotransplantation still faces many challenges in its application, including potential immunological problems, physiological incompatibility, and concerns about the risk of transmitting infections that can cause zoonotic diseases in humans (8).

3.2 Xenotransplantation Method in General

In performing xenotransplantation, there are several things that must be considered first. Some of these things are as follows:

1. Development of a suitable porcine xenograft

Initially, xenotransplantation focused on utilizing organs from non-human primates (NHPs). Despite having a close phylogenetic relationship with humans, NHPs were found to be incompatible due to several factors such as difficulty in generating gene modifications, ethical and biosafety issues. Therefore, many xenografts are now derived from pigs. The use of xenografts from genetically modified pigs has many advantages, namely that pigs are relatively easy to maintain, have similar organs to adult humans and can grow quickly. So based on this, pigs were identified as a possible source of xenografts.

2. Advanced immunosuppression protocol for xenotransplantation trials

Successful immunosuppression protocols should involve gene combinations that increase the duration of transplantation with the least amount of side effects in the recipient. Whereas immunosuppression therapy consists of plasmapheresis to remove pre-formed antibodies in the donor, targeting T-cells and B-cells to keep them low and underactive to avoid immune rejection of the transplant, complement protein inhibition, anticoagulants, and anti- inflammatory agents to avoid local transport of immune cells to the transplant.

3. Functional and metabolic capacity of xenografts

There are several differences in functional and metabolic capabilities that must be considered. Although in theory there are visible differences if the proteins produced by the species are genetically different which leads to failure of the graft to recognize rejection as the main cause of xenograft failure. One of the physiological changes triggered by xenograft is thrombotic microangiopathy and systemic consumptive coagulopathy.

4. Recipient selection

After going through the previous stages, organs with potential for xenotransplantation clinical trials were selected. Then potential candidates for xenotransplantation are selected. Where candidates

for xenotransplantation trials are patients whose waiting time is longer than their life expectancy and have no living donor detected.

5. Clinical xenograft trial

Clinical trials are conducted to see if the donor and recipient are compatible. In 2022, the University of Maryland reported the discovery of a life-sustaining porcine xenoheart. The transplant was performed on a human with a modified immunosuppression protocol and maintenance of co-stimulation blockade. However, after 8 weeks of transplantation his condition declined and died. So clinical trials need to be conducted to determine the effects.

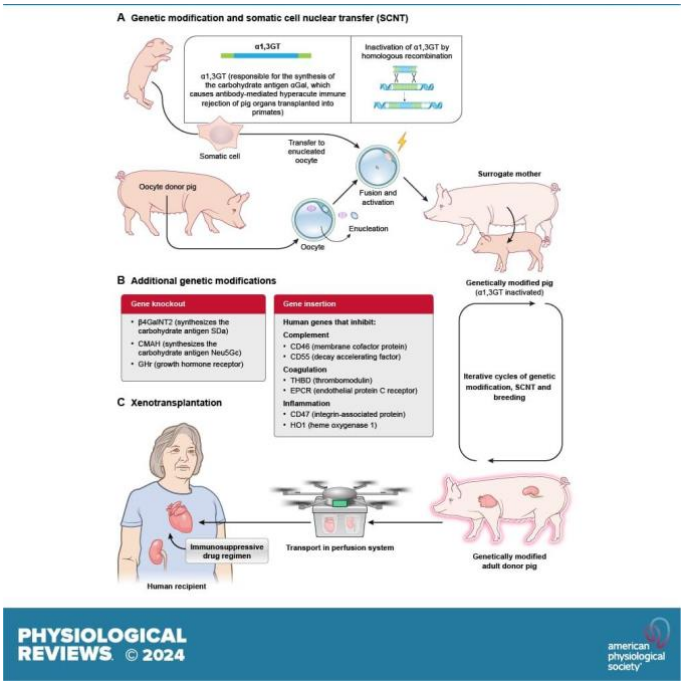

Figure 2. The process of genetic modification, somatic cell nuclear transfer (SCNT) and xenotransplantation applications using genetically modified pigs

This figure illustrates the steps in genetic modification, somatic cell nuclear transfer (SCNT) and the application of xenotransplantation, which is organ transplantation between species using genetically modified pigs as organ donors. This process includes inactivation of the α1,3GT gene to eliminate carbohydrate antigens that cause hyperacute rejection in human recipients. The nucleid of the genetically modified donor somatic cells were transferred to an inoculated egg, diffused, activated and implanted into a surrogate mother. The result is a genetically modified pig with better compatibility for organ transplantation. This cycle is repeated to ensure success and optimal compatibility (23).

Additional genetic modifications include the removal of certain genes, such as β4GalNT2 and CMAH, which produce immunogenic antigens, as well as the addition of human genes, such as CD46, THBD, and CD47, to improve the organ's compatibility with the human immune system. Once the organs from the genetically modified adult pigs are harvested, they are stored in a perfusion system until the transplantation process is performed on a human recipient. Patients receive immunosuppressive therapy to prevent rejection reactions. This biotechnological approach offers a potential solution to the shortage of donor organs, by creating a safer and more effective alternative source of organs (23).

3.3 Potential and Risks to the Medical World

Before xenotransplantation was applied to humans, many clinical trials were conducted on primates. This is to test three things that are important in the xenotransplantation process, namely (i) organ rejection from immune reactions and coagulant dysfunction, (ii) physiological incompatibility, and (iii) microbiological risks. To address these three considerations, preparations are made before methods such as multi-transgenic animals are produced. Research on physiological compatibility is still being studied, based on the short survival time of donor primates. The risk of microorganism transmission is controlled by breeding donor animals that are free of pathogens. However, there is a

particular risk in all pigs where the genome contains Porcine Endogenous Retroviruses (PERVs), which are viral particles that can infect human cells. Screening protocols for donor animals with low expression of PERVs are becoming more extensive with the development of strategies to prevent transmission of PERVs (7). The pathobiology of xenotransplantation has so far considered pigs as one of the potential organ and cell donors for humans. Factors such as availability in nature, potential to give birth, reproductive maturity, number of offspring, organ size, and cost of treatment are the benchmarks that make pigs potential candidates for xenotransplantation rather than baboons, which are primates like humans. Although primates; have high anatomical & physiological similarity to humans, baboons are animals whose availability in nature is very limited. It takes about 9 years to reach adulthood and its potential to give birth is very small compared to pigs. Furthermore, in terms of public acceptance and opinion, xenotransplantation from pigs as donor animals is more widely supported than baboons (6).

Among other animals that have served as donors are sheep; blood donors to humans in 1667 (2), rabbits; kidney donors to humans in 1905 (19), and non-human primate species; kidney, heart, and liver donors to humans in the 1920s to 1990s (9, 5). However, although non-human primate species are phylogenetically closer to humans than other animals, researchers have argued that primates are not a suitable donor source for xenotransplantation due to ethical concerns, high risk of infection transmission, breeding difficulties, organ size differences and other impracticalities. Therefore, since the 1990s researchers have been working to develop xenotransplants from pig organs, which are now considered the most appropriate candidate species (6).

In an effort to reduce organ rejection and coagulation dysregulation in xenotransplantation from pigs to humans, gene-modified donor animals were developed through a series of genetic engineering processes. Genetically modified pigs are intended to bridge the molecular incompatibility between donors and recipients of different species. With the revolution of genetic engineering technologies such as CRISPR/Cas9 (Clustered Regular Interspaced Short Palindromic Repeats-Cas9), xenotransplantation methods have progressed rapidly since 2009. With CRISPR/Cas9, a wide variety of genetically modified pigs have been produced. The edited genes can be customized according to xenotransplantation interests and can be obtained more easily and quickly (18). An example of a gene inserted with the CRISPR/Cas9 method is PERV *inactivation*, which functions to inactivate *Porcine Endogenous Retroviral Virus* to minimize the occurrence of xeno zoonosis (22).

3.4 Xenotransplantation Cases

Prior to the success of xenotransplantation, there were xenotransplantation failures. On October 26, 1984, Leonard Bailey performed an orthotopic baboon heart xenotransplantation on a 12-day-old baby named Baby Fae, who was born with hypoplastic left heart syndrome. The surgery went well, but 20 days later the baby was pronounced dead. This was due to organ rejection (3). In addition, another cause was the absence of a size match and immunologically immature considering he was only 12 days old. This xenotransplantation failure led to a short pause in xenotransplantation (27).

Organ xenotransplants that have so far been successfully performed from pig (genetically modified) donor animals to humans include heart, kidney, lung and liver xenotransplants. The survival time of humans after receiving these organ donors shows different periods. In *non-life supporting* heart donors, it shows a range of 159 to 945 days (17). Meanwhile, for *life-supporting* heart donors, humans survive for 195 days at most (14). For kidneys as *life-supporting*, the longest time humans survive is 499 days (13). Lung and liver donors have been shown to last 14 and 29 days, respectively (26, 31, 15). With a better understanding of genetic engineering technology, it can be predicted that the period of human survival after xenotransplantation will become longer.

3.5 Ethical and Islamic Perspectives on Xenotransplantation

In medicine, xenotransplantation is an alternative solution that can address the critical and ongoing problem of insufficient supply or availability of human organs and cells for clinical transplantation for patients in need. The development of genetic engineering, for example in pigs, has shown rapid progress in overcoming the problem of immune resistance to xenotransplantation itself. Antibody and human cell rejection of donor animal organs or cells has largely been overcome (4). With the development of science, technology and medicine, challenges such as coagulation dysregulation

during xenotransplantation due to molecular incompatibility between animals and humans have become the main focus to be solved. By doing so, xenotransplantation becomes a solution that can be offered more wisely to humans to survive longer or improve the quality of life with transplantation methods.

The discussion on xenotransplantation does not end with medicine. After knowing that this method can be a solution to overcome diseases that require donors, ethical and religious perspectives need to be considered. In the Law of the Republic of Indonesia Number 36 of 2009 Article 66 section five on Disease Cure and Recovery has been explained regarding xenotransplantation where the article reads, 'Cell transplants, both of human and animal origin, can only be carried out if their safety and usefulness have been proven' (1). Then, based on Article 64, it is said that, 1. healing of disease and restoration of health can be done through organ and/or tissue transplantation, implantation of drugs, and/or medical devices, plastic and reconstructive surgery, and the use of stem cells, 2. transplantation of organs and/or body tissues as referred to in paragraph 1 is carried out only for humanity and is prohibited from being commercialized, 3. organs and/or body tissues are prohibited from being traded under any pretext. Broadly speaking, the Law regulates regulations regarding transplants (including xenotransplants) so that they are always utilized wisely and not abused (24).

In general, there are different views among religious leaders when asked about the law of transplantation. The majority of scholars allow it, while some do not. Most of those who allow it, such as An-Nawawi, Zakariya Al-Ansari, and Yusuf Qardhawi require several things in the implementation of this transplant, such as if it is not urgent then the transplant must be carried out with pure goods or organs, transplants are carried out only when it is urgent and there is no other way to cure except by this method, then it does not cause greater harm or *dharar* either for the donor or the recipient. While Mufti Muhammad Shafi'i, a scholar from Pakistan and Dr. Abd As-Salam As-Syukri, a scholar from Egypt argue that transplantation is not allowed based on principles and considerations such as the sanctity of life (human body), the assumption that the human body is a trust, the treatment of the human body as a material object, the preservation of the glory of life, and efforts to avoid doubt (12).

Furthermore, regarding the Islamic perspective on xenotransplantation, especially from pigs, there are various opinions because in essence pigs themselves are haram, whether it is for consumption of meat, skin, or blood. On the other hand, transplants from pig organs and cells for humans can provide benefits to society. But on the other hand, the transplant donor is an animal whose law is haram. The contextual approach promoted by Abdullah Saeed concludes that the prohibition of pigs referred to in QS. Al-Baqarah: 173, QS. Al-Maidah: 3, QS. Al- An'am: 145 and QS. An-Nahl: 115 is in the context of consumption. However, the mufassirs (exegetes) differ in their opinions on other uses beyond consumption.

Referring to technological developments such as the current phenomenon of xenotransplantation, a statement can be drawn that the use of pig organs for transplantation to humans (xenotransplantation) is permitted. The statement is strengthened by the wording in QS. Al-Baqarah: 173 which mentions the context of emergency in this utilization. Scholars who allow xenotransplantation are guided by *Al-Ithar* (impact) as part of the good. Meanwhile, other scholars who prohibit it rely on the prohibition of *Taghayyur* (change). The group of scholars who allow it do not say it absolutely but *muqayyad* (conditional), namely that it can endanger life. If this condition is not met, then the majority of scholars are of the opinion that it is haram to use unclean objects as medicine (21).

3.6 Ethics Matrix

The ethics matrix is a theoretical instrument designed to assist individual and group decision-makers in making decisions about moral acceptability and regulatory control. In the ethics matrix some *prima facie* principles are applied to specific interest groups. These principles include respect for welfare, autonomy and justice which form a column in the ethics matrix. The ethics matrix was designed with the aim of assisting users in identifying ethical issues that arise when using new technologies and assisting in making intellectually defensible decisions (16).

Table 1. Ethics Matrix in Xenotransplantation Implementation Using Mepham's Ethics Matrix Concept

	Justice	Welfare	Autonomy
Patient	Ensure that xenotransplantation is accessible to all patients in need	Ensure that xenotransplantation provides benefits and does not pose risks that harm the patient	Ensure that the patient gives informed consent to any xenotransplantation procedure performed and is aware of the

	Justice	Welfare	Autonomy
			xenotransplantation procedure
Family	Ensure that the patient's family benefits equitably from xenotransplantation	Ensure that xenotransplantation can empower the patient's family to provide support to the patient	Ensure that the patient's family has the right to privacy in the xenotransplantation process
Animal experiment	Ensure that xenotransplantation procedures are fair to animals and do not pose risks after the transplantation process	Ensure that the xenotransplantation procedure does not harm the animal and that the procedure is performed by skilled personnel	Be sure to pay attention to animal welfare and freedom from suffering when xenotransplantation is performed
Civil society	Ensure that that the application of xenotransplantation is equitably utilized by all civilians	Ensure that civil society can give its views on xenotransplantation.	Ensure that the privacy rights of every xenotransplanted individual in civil society can be strictly maintained

Based on the ethical matrix in table 1, the practice of xenotransplantation can be seen from the perspective of the various parties involved, namely patients, patients' families, experimental animals and civil society. Where xenotransplantation refers to the transplantation of organs or tissues from different species. So that there are ethical considerations that need to be considered by each part involved.

Each part has rights and responsibilities that must be fulfilled, namely the patient has the right to safe and effective treatment. So that patients must know the benefits and all potential risks regarding xenotransplantation. The patient's family must be involved in medical decision making, especially if the patient is unable to give consent. In addition, families also have the right to know the potential risks and expected outcomes of xenotransplantation. The use of experimental animals must respect animal welfare principles where the methods used must reduce animal suffering. Civil society also has the right to access and know information about xenotransplantation practices.

4. CONCLUSION

Xenotransplantation could potentially be an alternative solution that can be used to address the scarcity of transplantable organs for humans. The animal organs to be used can be altered to be more compatible through genetic engineering. This could potentially save patients with organ damage. Although there is a risk of immune rejection and possible zoonotic infections (animal-to-human diseases) due to xenotransplantation. These risks can be reduced with further research to create animal organs that fit the human body. In Islam xenotransplantation is allowed if it is done to save lives and not to abuse the animal.

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