

A Review on Background of Xenotransplantation, Xenosis, Advantages/Disadvantages and Ethics of Xenotransplantation

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ABSTRACT

The recent unavailability of donor organs for transplantation in patients with life-threatening organ failure is demonstrated by the situation with kidney transplantation. The expectation of many people is associated with organ transplant globally. In 1907 A. Carrel proposed that a large supply of tissues and organs makes it possible to treat people which are ill early before they reach to severe condition by using animals as organ donor. So there is no need for patients to wait for the organs to transplant and this transfer provides the permanent alternates of organs. Clinical cross-species xenotransplantation has a long history going back to blood transfusions across species in the 17th century. When normal microbes that are produced by animals act as foreign substance for human against which they generate an immune response and this pathogen possess harmful effects on human so this phenomenon is described as xenosis. By the advantages of xenotransplantation the dangers that are associated with infections overcomes. Although increased danger of infections in transplantation is caused by many aspects. There are some ethical concerns linking to probable human receivers of animal organs and also for animals as bases of organs for human beings.

INTRODUCTION

The recent unavailability of donor organs for transplantation in patients with life-threatening organ failure is demonstrated by the situation with kidney transplantation. Transplantation of a kidney from a late or alive donor is ideal treatment for patients with irreversible kidney failure (end-stage renal disease, ESRD). For at least a quarter of a century, the restrictive factor prohibiting effective transplantation for thousands of wait-listed ESRD patients, and thousands more never listed, has been the relative shortage of available kidneys [1].

The expectation of many people is associated with organ transplant globally. In 1907 A. Carrel proposed that a large

supply of tissues and organs makes it possible to treat people which are ill early before they reach to severe condition by using animals as organ donor. So there is no need for patients to wait for the organs to transplant and this transfer provides the permanent alternates of organs. Transfer of organs and cells from the species that are different from humans is named as xenotransplantation [2]. These organs and tissues may be unaffected against the HCV and human immune deficiency virus that are common foreign substances which infect the humans.

There are some benefits related to xenotransplantation are present such as it is performed to escape the risk of harmful effects of humans own viruses and pathogens. An example of liver and bone marrow of baboon's transplantation into a human for the treatment of acquired immunodeficiency syndrome and hepatitis that is caused by the virus. This type of transplantation is projected and the treatment of giver and receiver before the transplantation is carried out to reduce the risk of infection, removal of pathogens and to induce the immune system acceptance. Animals are genetically modified for transplantation of organs to avoid the threat of rejection and to contain the genetic material that shows the beneficial importance for the receiver of organ.

The drawbacks of xenotransplantation includes: the immune system of the human that generate responses against the transplanted organ and the possible risk of the transfer of new infection causing microbes into the human from animals. The probable applications related to achieve the xenotransplantation and difficulties that are attached to accomplish this transplantation in human recipients gives the advance to study.

By understanding the human immune responses against the transplanted organ we can suggests the new ways that helps to overcome the difficulties in xenotransplantation. Understanding of usual and induced response of immune system against transplantation also gives fresh visions about the purposes and mechanism of resistance. (Cascalho & Platt, 2001) [3].

BACKGROUND

Clinical cross-species xenotransplantation has a long history going back to blood transfusions across species in the 17th century,(D. K. Cooper, 2012) [4] when Jean Baptiste Denis began the clinical practice of blood transfusion from animals

to humans (Roux, Sai, & Deschamps, 2007) [5]. Following the revolutionary surgical work of Carrel, who developed the technique of blood vessel anastomosis, several attempts at nonhuman primate (NHP) organ transplantation in patients were carried out in the 20th century. For this work he was awarded the Nobel Prize in 1912 (Hamilton, 1986) [6]. The modern history of xenotransplantation in the United States is generally thought to begin in 1963 to 1964, when Keith Reemstma transplanted kidneys from chimpanzees into six patients with renal failure [6]. One patient returned to work for almost 9 months supported by a pair of chimpanzee kidneys [7,8]. In 1964, James Hardy was determined to carry out the first (unsuccessful) heart transplant utilized a chimpanzee as the 'donor'[9]. Several attempts at solid-organ xenotransplantation have received wide coverage in the lay media. For example, in 1985, Leonard Baily transplanted a baboon's heart to a baby born with hypoplastic left heart syndrome (Baby Fae) (Bailey, Nehlsen-Cannarella, Concepcion, & Jolley, 1985) [10], hoping that the newborn's undeveloped immune system would tolerate the xenograft. The child survived less than 4 weeks, and subsequent press coverage was very negative. In the early 1990s, Thomas Starzl transplanted baboon livers into two patients with HIV infection and advanced hepatitis B, who survived 27 and 70 days (Allan et al., 1998; D. Cooper et al., 2018; Starzl et al., 1993; Starzl et al., 1964) [1,7,11,12]. The procedure of cardiac allotransplantation was later established by Barnard and his colleagues in 1967(C. N. J. S. A. M. J. Barnard, 1967) [13], who later also carried out two heterotopic cardiac xenotransplants, using a chimpanzee and a baboon as 'donors' (C. Barnard, Wolpowitz, A. & Losman, 1977) [14].

Understanding of patients that have weakened immune system mentions that the new microorganism might appear as a source of infectious pathogens, for humans and as well as other creatures. Because transfer of infection causing agents is very efficient so xenotransplantation has risks associated with different diseases. Viruses are the most common pathogen that is transmits through the implants.

Pigs attain an adult size that makes organs potentially compatible with those of an adult human. The life expectancy of pigs (around 30 years) also is compatible with duration acceptable for xenotransplantation products for use in adult humans (Taubenberger, Reid, Krafft, Bijwaard, & Fanning, 1997; Wells et al., 1991) [15,16]. Pigs are mostly use for the purpose of xenotransplantation and they are slightly similar to humans that are why organs of pigs are used as a basis. Although other

animals such as monkeys and chimpanzees are closely related with human beings but risks that are associated with their use as an organ donor is restricted. The danger of transfer of infection causing agents, difference in size of counterparts, expensiveness and complications has disqualified this possibility. FDA prohibits the use of nonhuman primates as a tissue and organ givers for the benefits of humans because Doubts appears concerning with the possibilities that are related to the practice of these animals for transplantation. However on the basis of immune system hogs are not similar with humans but they offer a proper size counterparts and genetic modification can be done for the expression and suppression of particular inheritable factors that are related to the grafting.

Early biological worry is concerned with the pig-generating pathogens or parasitic microbes. Bacterial species like *Streptococcus suis* might not be described without difficulty there are some complications are associated with the description of this bacteria by furthestmost scientific biological research laboratories. Although the capability to eliminate the disease causing microorganisms and pathogens from groups of pigs is intended for the use of the pigs as a source of organ givers and the concerned is mostly related with infectious viruses. Hypothetical worries concerning with the transfer of porcine endogenous retroviruses that gained the interests of many biologists because this is a unique substance for causing infection in humans that are transferred from pigs. Other possible infectious agents from pigs are also categorized for excluding and preventing the infections that occurs because of them (J. A. Fishman & Patience, 2004) [17].

Xenosis

When normal microbes that are produced by animals act as foreign substance for human against which they generate an immune response and this pathogen possess harmful effects on human so this phenomenon is described as xenosis (J. A. J. K. I. S. Fishman, 1997) [18]. Transplanting organs from nonhuman species into humans becomes a possible difficulty. It is also a difficult task to recognize these pathogens, novel medical conditions and different effects of these microbes on patients that receive the organs from animal and they have relatively weakened immune system. Zoonosis is a concern because of the potential transmission of infectious agents, including porcine endogenous retroviruses, with the pig organ to the human recipient and possibly to those who come into contact

with the patient (Denner, 2016; Onions et al., 2000) [19,20].

By keeping the view on mind about allotransplantation (The transplantation of living organs, tissues, or cells from one human to another or between individuals within the same species) (Battista, 1998) [21] an approach is suggested to decrease the dangers of microbes that are present in animal donor and possess negative effects on humans. Microorganism that are act as pathogens for humans are removed from the groups of donor animal by genetic modification [16].

Importantly, for the first time, xenotransplantation allows modification of the donor and not only treatment of the recipient. Genetic engineering of the organ-source pig has largely involved (i) deletion of expression of one or more of the three key pig antigens, and/or (ii) insertion of a human transgene that provides protection from human complement and/or coagulation activity (Butler, Tector, & surgery, 2017; D. K. Cooper, Ekser, Ramsoondar, Phelps, & Ayares, 2016) [22,23]. Deletion of expression of two or all three key pig antigens has been achieved by simultaneous knockout of their respective genes [24,25].

With the new technology now available (e.g. CRISPR-Cas9), it is becoming quicker and cheaper to achieve multiple genetic manipulations in pigs, (Meier et al., 2018) [26] thus accelerating progress towards clinical implementation of the technology (Butler et al., 2017) [21].

ADVANTAGES

By the advantages of xenotransplantation the dangers that are associated with infections overcomes. Although xenotransplantation addresses the key infective dangers presently opposed in human allotransplantation (Platt, 1998) [27]. (both organ donor and receiver are humans), this becomes an important experimental feature.

Various advantages of xenotransplantation are:

- Watchful bacteriological and viral monitoring and analysis of animals are performed before the organ transplantation but in case of transplantation that includes only human improper monitoring of human organs is performed before the transfer of organ.
- Resistance is induced in tissues and organs that are used for transplantation against the infectious causing agents that are derived by humans such as human immune

deficiency virus, human T-lymph trophic virus, HIV and cytomegalovirus. E.g., Piggish cytomegaloviruses do not show any harmful effects on monkey organs. May be these type of primates do not contain the cellular organization that is required for the replication process of virus in human beings.

- External immune responses are suppressed for restricted period by inducing the acceptance in immune system so when transplantation practices are performed it decreases the danger of any adaptable infection.
- There is no need for patients to admit in hospitals for long period of time because the transplantation of recipients occurs on time when it is needed. It also decreases the danger of infections which are caused by microorganisms that are resistant to antibiotics and are commonly found in hospitals [17].

DISADVANTAGES

Increased danger of infections in transplantation is caused by many aspects that are:

- The organs that are transplant is act as a tolerant tank that avoids the host resistances and transfer the infectious diseases into humans and they do not require any direction for the transfer of infections.
- Understanding about the effects of microorganism that are transferred into humans is not satisfying so it becomes the cause of complication in the case of patients that have a weakened immune system.
- Incapability in to the recognition of the new medical disorders which are caused by the microbes that are transferred by the animals.
- Infectious agents that are produced by the donors of transplantation do not cause the infection in same species but can cause infection in the species that are different from them and also mutating the genome that becomes the cause of new features obtain by the human.
- Mismatches between the giver and receiver tissues causing reduction in the human immune reaction against any infection in the organs that are transplanted from animals [28].

CLINICAL TRIALS

The main concern of these trials are examining and recognizing the probable diseases difficulties in the therapeutic laboratories by the help of performance of the medical trials. Surgeons provides medical precautions and maintenance and also provide limited medical test centers. It is necessary that the person who need transplantation knows about the potential consequences and transfer of infections by the organs that are receive from animals and also know about the effects on the fitness and healthiness. They also make a plan for first assortment, handling and storing the medical samples. The main requirement is separation of the receiver of organ, statement of the fitness of community and skilled experts.

Consultant of community fitness should maintain inaccuracy of regular data and storage of samples. They also carry out the appropriate examinations of infectious occasions that are caused by the transplantation of organs from animals and also communicate and discuss the information with the suitable skillful experts. The need for the base group improvement and clinical analysis will differ with confined guidelines. Worthy industrial trials and worthy techniques of the laboratories are taken into consideration because value of developing procedures and methods of laboratories are noticeably described and measured, difficult procedures are also wisely authorized [29].

Ethics

➤ Ethical concerns linking to probable human receivers of animal organs:

The main concern is that the patient that is near to last phase of organ failure is also treated like other patients and he/she also eligible for the similar rights. Disrespect of those people is considered as wrong and their approval is as important as others. Although there is possibility of not knowing about consequences is also present because novel infections are occurred in individuals that receive the organs. Along with the danger that is related to the development of new infection the danger of swinish infection in the receiver of organ is also becomes a cause of concern. The swine is fully examined and monitored before it donates the organ so the danger of infection causing pathogens is reduced. If they contain any infection causing substance it is specie specific microbe that only cause infection in swine but incapable of causing infection in humans. Practices are done on pigs to remove identified microbes that is cause of infection. It

is sensible and satisfactory to take organs from swine that are pass through different medical tests and all recognized pathogens are eliminated. It is necessary to inform recipient about the infectious causing agents that are transferred from pig to humans such as porcine endogenous retroviruses. It is also included in the rights of patients that if they want to stop their medical trial so it must be stopped. If receiver gets organ from pig so they are in danger to possess the swinish infection throughout their life. If the receiver will give the approval of their post-mortem after the death so it becomes easier for scientists to identify and recognized new pathogens and microbes that are capable of causing infection after xenotransplantation which are still unknown medically.

➤ **Ethical concerns concerning to the practice of animals as bases of organs for human beings:**

Different opinions of people are in concern about animals some peoples thought that animals are source of benefit for humans and are used for the production of different goods, exploration and investigation purpose and also serves as the food source while other are veggies they only eat vegetable and they are against the production of any type of goods from animals and also strictly against for the use of animals for investigation purpose. Some people thought that animals should be treated according to the demands of people and some people thought that animals also have rights same as humans. The sensible thinking is that humans show humanity towards animals and give some respect to animals but animals are not allowed to have same rights as humans. One individual of any other specie is not poorer than other individual of different species such as if fit chimpanzee is used to give its organ to save the life of a brain-dead human that is not able to survive and feel anything from a long period of time it is wrong because the ape was the main fellow of his specie and may be it is valuable animal in this universe and he is also intelligent and shows emotions but we considered a brain-dead individual as compared to this nonhuman primate. The swine is used as a food source but now humans use them to treat different kinds of human diseases. Use of pig organ donor is common in xenotransplantation. In different cases pigs are used to provide insulin and heart valves for the treatment of humans and also used in skin grafting for the patients that are burnt in all these situation they have to be expired. Individual who have no concern with the killing of pigs accept this type of treatment and do not raise any objection against these and they are convinced to use pigs as a main basis for the

transplantation purpose.

If pig heart and all other organs are donated and they were killed in a large number so the risk of their extinction is increases in future. Only veggies that does not eat and use animals for any purpose raise the objection against the use of pig organs for transplantation purpose. Breeding of swine for use in transplantation is occur and management authorities are keep check and balance on those people who did this to confirm the good carefulness and housing of these animals. It is necessary to keep these animals safe and provide good care to them and monitoring of these pigs should be performed not only to check that the organ is free from infectious agents but also to decrease the dangers of infections in them. Good care is needed to keep them infection-free environment and their national condition is also an important aspect that is also required the concern. When animals are used as a food source it is not become a big issue but when they used as a source for transplantation purpose they are treated by humans and medical techniques so many of these animals cannot survive in these conditions and when they anaesthetized they will die sometimes. The opinions that are arise from the use of swines for the transplantation purpose are less as compared to those objection that are raised against the animal usage for medicinal study and for their consumption as meat source.

Genetically modified pigs are used that are modified to eliminate infectious agents that effects the humans and they also shows some human genes. Human proteins are produced in these pigs in a less quantity and this is considered as a destruction of the specie limitations. it is proposed that genetically modified animals have undesirable effect on environments because if these types of pigs are mate with uninhabited species so they can generate a different kind of variety that may be harmful. To reduce this danger it is suggested that these swines are kept separate from uninhabited swines. Genetic manipulation is against the ethics. The consultative authorities give the permission of some small kind of genetic manipulation for xenotransplantation but there are some restrictions are also recommended. The genetic modification that is allowed should be performed under two conditions; intolerable practices should not performed on animals that have harmful effects on pigs fitness and the benefit of these animals are keep in mind, and the methods that is applied on animals must not be against to the ethics. Instructions are apparently made against inducing the changes that altered the brain that may change the thoughtfulness and intelligence capacity of

the hogs and sometimes this may also have negative effects on receiver of the pig organ (Smetanka & Cooper, 2005) [30].

CONCLUSION

Xenotransplantation is used for the treatment of humans that suffer from organ failure. It is a very useful and valuable approach as compared to the allotransplantation. This reduced the risk of infections that are caused by human pathogens. Although xenosis is occurred sometimes but it is still a beneficial treatment for the humans. The major benefit of transplantation is that if any human organ is not found at the time of need so animal organs are used for transplantation most commonly pig's organs and many lives are saved by this method. There are some risks are associated with the xenotransplantation that are methods that becomes the cause of spreading of infection. Some ethical issues are also associated with this approach. If individuals, skillful authorities and biologists collectively discussed and work on these risks and issues so they will form a strategy or plan to overcome these problems and xenotransplantation becomes an effective strategy.

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