Opinion

Ethics of Tissue and Stem Cell Transplantation

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ABSTRACT

Tissue and cell transplantation are regarded as a popular procedure in clinical sciences, prospecting a new horizon for several incurable diseases. Along with its usefulness, many ethical concerns accompany this development. The ethical issue of organ transplant is unique to the source used which includes: living related, living unrelated, cadaveric, and xenotransplant.

Obtaining organs has a separate set of ethical concerns which are discussed under two headings, namely salvage and donation. Then there is the issue of organ marketing and the ethical, social, and economical issues it encompasses. All these are active areas of debate, and we have touched upon them by turn.

This century has brought a new aspect of transplantation into the light, stem cell transplantation. Here we present some work done recently on mesenchymal stem cells and their outcome. These cells are now being employed in the therapy of some incurable ailments.

It seems this kind of transplantation, although possessing its own range of issues, could prove to be the way of the future.

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INTRODUCTION

In recent years, tissue and organ transplantation have come to thrive and today different organs are transplanted routinely. Because of its nature and rapid development, this new treatment has raised many ethical concerns among society at large.

The bioethical debate of organ transplantation has come up recently, but the story goes back to the first transplanted kidney in 1954.

The ethics of organ transplantation can be divided into four categories in regard to the source of the organ: living related donor, living unrelated donor, cadaveric donor and xenotransplantation (donor from other species)

Of course to these we must add the new development and use of stem cell as a new source. Each group has its own specific ethical problem that requires special attention and consideration regarding different cultural and religious backgrounds and populations.

The general topics that must be considered for transplantation programs are as follows:

1) Deciding when a human being is dead (in case of cadaveric donors)
2) Deciding when it is ethical to procure an organ
3) Deciding how to allocate the organ once it has been procured

As mentioned, one of the most crucial issues is the cultural and religious beliefs unique to the population in mind. This is true especially in regard to the cadaveric and xenotransplantation methods.

Living related and more importantly, living unrelated donor transplantations have a variety of unique aspects pertaining to various organs that must also be taken into consideration.

Although there are restrictions, but most religion and cultural groups do not have an outright, uncompromising opposition to organ transplantation.

We will not be able to have a comprehensive review of all the ethical aspects of transplantation in this limited space; therefore we shall focus our discussion on some of the essential points.

First, we will have a look at the cadaveric donor issues:

Here we have two important points to consider

1) The definition of death
2) The method of procuring the organ (salvage or donation)

Definition of Death: The definition of death does not directly concern our discussion and needs a separate paper. The public policies of issues raised by the definition of death are more complex than they might appear at first.

The other issue we are faced with is the rapid development of science and the changes it invariably brings into the definition of a dead person, due to the new horizons and limits achieved every day. In recent years, the brain oriented definition of death has been accepted by medical corps, but there is growing doubt about the present agreement of "when is the brain really dead?".

All major religions reveal certain differences of opinion over a shift to the use of brain oriented definition of death, a shift important if organ procurement is to be facilitated with it. But as a whole, all major religions have accepted the criteria of brain death (1).

In 1981, the Islamic code of medical ethics of the international organization of Islamic medicine gave a vague verdict on the subject by announcing "To declare a person dead is a grave responsibility that ultimately rests with the doctor" (2), however it mentions nothing against the use of the brain criteria of death.

There were reservations among Muslims about death defined as "lack of brain activity" rather than the conventional definition of respiratory and cardiac arrest. These issues were discussed at a seminar entitled "Human Life: Its inception and its end as viewed by Islam" (3). The published reports of the result of this meeting conclude that the Qur'an does not define death; the participants came to the conclusion that when the area of the brain responsible for vital body functions-which they defined as the brain stem- is lifeless, the patient can be said to have died (They mentioned that while the brain stem is still alive, all efforts must be done to revive the person. If the brain stem is dead, even when signs of activity are still visible in the bodily organs – but there is no hope of reviving the patient – then the patient is considered to have withdrawn from life), and so procuring the organs are permitted (4).A similar conclusion was reached at the 3rd international conference of Islamic Jurist meeting in Amman, Jordan in October 1986 (5).

In Islam the body is sacred – entrusted to one's care on earth, harm must not be done to it, in life or in death. Although there have been considerable debates within various societies and sects, procurement by donation has been considered acceptable by many Muslims. In fact, similar to Judaism, the donation of organ in Islam is seen as a duty towards a fellow human being (2, 3).

According to the Islamic code of medical ethics "The individual patient is the collective responsibility of society, which has to ensure his health needs by any means inflicting no harm on others. This comprises the donation of body fluids or organs, such as blood transfusion to the bleeding, or kidney transplant to a patient with bilateral irreparable kidney damage, a duty that donors fulfill on behalf of society" (7).

As we have seen, although there is no major restriction of cadaveric organ procurement, but there are still objections to the different methods of procuring the organ.

Salvage or Donation: There are two alternatives for organ procurement: Donation and Salvaging. Most major religious and cultural traditions of the world do not have a clear-cut, principled objection to life-saving organ transplant (1). The basic approach of a society to transferring organs from a potential organ source to others who need these organs must be well established. Of course all this must be done in the context of the beliefs encompassing the society in question.

Salvage: Under salvaging schemes: "Cadaver organs can be routinely "salvaged", taken without any formal consent when they are needed as a social resource" (8). The dead body would simply be presumed the property of the state when the body could serve a useful purpose. Most religions and societies are opposed to this idea (1-3).

The other Alternative is: The major question now (in the case of cadaveric donors) is: Are organs the property of society to salvage and use if it sees fit? Or do they rightfully belong to individuals and must be presented as gifts before another can use them?

After some resistance in the 1970's, the western society made an important choice by accepting human to human transplant as morally permissible. More critically, we tend to feel a wrong is committed if the individual's will is not honored, even if we believe that the individual can not know about or feel this when it does occur.

Donation: The assumption is that an individual has a right over and against the state, including the right to bodily integrity. Holders of this view insist that this right does not cease at death. Under this approach, the deceased retains the right to determine how his/her body is treated, even after death. This is also the view held by most major religions (1-3, 6).

In Japan, by the new transplantation law, explicit consent of both the deceased and family is required (9).

It seems that no major religion or group actively opposes organ procurement. Each religion however holds a certain position as concerns the ethical norms that would determine the way the organ is procured and allocated The goal should be to provide a moral frame work for thinking about transplantation as a matter of public policy – that is when both consequences (efficiency) and just allocation (equity) are taken into account.

In a national transplant program, the law requiring both efficiency and equity should be in effect.

Although promising, this method did not work as well as expected. The donation model (Someone who accepts to donate his/her body parts after death) does well in stressing the importance of human rights, the only problem is that it doesn't work! The policy of taking organs from the individual or surrogate only after donation has not provided eno*ugh organs.* In the year 2000, there were over 67000 people on the waiting list for organs in the US alone; about 4000 cadaver organs were recovered, together with a little over 3000 from living donors, for a grand total of 8000 organs only. The situation was not better in other countries (1-8).

Clearly, the need is great and the disparity between procured and needed organs is growing rapidly, and meanwhile the number of patients dying while still on the waiting list is getting out of hand. Although many will die for lack of organ, a considerable number of people willing to donate an organ never make the effort to fill out a donation card. What is needed is the implementation of a more suitable option for facilitating donation.

Therefore some countries proposed the model of organ salvage as a solution, if there is no objection from the deceased person. Another model is living unrelated donor models, as some countries have already experienced (9-11). The problem with this latest model is opening the doors to an organ market, if it is not well organized.

Marketing of Organs: Experiences show that cadaveric or living related donation cannot provide enough organs for transplantation. Considering the waiting list and the continually growing pace of patients, some proposed another way of supplying organs to match the demand more closely. They called for a market for organ donation. Of course, our language would have to change from "donation" to "sale" of organs. This model needs an eligible organization (not broker), governmental or NGO, to take charge for the responsibility of payment or more properly compensating for the donor, without any direct contact between donors and recipients (Iranian model (12, 13)).

The Ethics of Marketing Organs: A well presented argument in favor of markets for organs being more suitable is difficult to refute. True, there may well be cases in which people would be desperate enough to sell a kidney, a liver, or even a lung lobe. There may even be so desperate as to be enticed to sell a whole liver, lung, or heart - realizing that they would die but their family would be spared an awful fate. But let us limit our attention-for now- to proposals of selling a single kidney.

Assuming that the vendor is an adult who is mentally competent and has been adequately informed about the risks and benefits of selling a kidney and after careful consideration has concluded that he/she prefers to sell the kidney and do something more useful with the money; it cannot be that such a person always calculate their interests incorrectly. Some people would really be better off with the money than their second kidney (they may be able to act more morally with the- taking care of loved ones in desperate need). Why should our society prohibit such decisions? Why

should we make such sales illegal! We need an argument that over rules the enlightened self interest of such sellers.

Moreover, many of the proposals to use markets to encourage organ availability do not rely on sales from living persons. They involve economic incentives to encourage actions that increase the supply of cadaver organs.

Marketing of organs is still controversial, but the growing need for organs due to insistent shortage and the growing waiting list, obliges us to find an alternative way. Although there were severe objections to the Iranian model (which will be presented in a separate paper) at the beginning, with the success of this model and the elimination of the waiting list (13), recently the view has changed and most countries including the USA are proposing a financial reward for supplying cadaver or living organs(1). The funds would come from the government or be accepted by Medicare or a welfare system.

Living Donor Transplant: When the early kidney transplantation started, organs were routinely procured from living related donors. Since the brain based criteria for death has been adapted in the early 1960s, all countries involved in transplantation have shifted to cadaveric donors. Since controversies still exist on the death criteria, and all countries suffer from a severe shortage of available organs (from cadaver and living related individuals), and the science of immunosuppression does not yet allow for routine xenotransplantation, most organs must be obtained from living unrelated donors for the time being.

Two major ethical questions arise from organ donation of living persons:

1) Under what circumstances can organs be procured from a living donor?
2) What consent or approvals are necessary to procure the organ?

If an organ donation is harmful and life threatening to the donor, we should not even consider taking it from a consenting related donor. However if the procedure and the absence of the organ, like that of a kidney is not a life threatening matter, then procuring it, even from an unrelated but informed individual poses no problems. In such cases, why should the donor not be compensated for what he has done, or be expected to do so for free? Is the transplantation team (doctors, nurses, pharmaceutical firm, hospital, etc...) giving their service and products for free? Why should the only person not being paid be the individual sacrificing a body part? This could also be true for cadaveric organs (the reward could somehow be very helpful to the surrogates and dependants).

Finally, with the development and progress of new immunosuppressive drugs, today the risk of donor/recipient incompatibility has been minimized and rejection has been lowered to the level of matched related organ transplantation. Therefore, the unrelated transplantation from cadaveric and more recently, living unrelated donors, has been growing rapidly. We can observe in recent years- in countries where cadaveric transplant was not possible- a rapid increase of living unrelated donor organs accompanied by the last from of introduced organ procurement, namely, "gift rewarded living unrelated donation".

The ambiguity of this model is great, but, this method could eliminate the long waiting list. The phenomenon and method of living unrelated donation will be discussed in another article, so I will not elaborate on the subject here.

It is the right of a person to become a donor. If competent persons may donate organs to families, friends, and even strangers as an act of charity, without violating any principle, then why should this not be extended to those willing to donate in return for some means of compensation (reward)?

Ethics of Xenotransplantation: Many ethical problems are raised by xenotransplantation. Most of them can be resolved; however, the most important are the virus related issues, which concern the recipient as well as society as a whole. This is the most crucial and yet difficult issue to surmount.

Over the past several years, increasing concerns have been expressed about the transmission of viruses from animals to humans in the process of xenotransplantation. Some of these concerns about primate organs sources have been mitigated by the development of transgenic pigs as a potential source. Pigs are easily bred and offer an anatomical and physiologically fit source for human transplant. Still, although a small risk exists about virus transmission from pig to humans (those endogenous for pigs but pathogenic for humans) but they can be propagated from the receiving individual to other humans. Therefore, viral recombination could pose a potential threat.

Although recent observations encourage the development of xenografts using pigs, it would be a mistake to make any final judgment or decision about the outcome of this debate (14). Especially in the present time, society should know the risks and be advised about the use of such a transplantation.

A New Topic: Having an overview of the different aspects and forms of organ procurement and transplantation, within the scope of new technology and developments in science; we will now focus on a new aspect of organ transplantation - or in better words, organ repairment – by using the new available source and method, the human stem cell repertoire.

The use of human Stem Cells (HuSC) in research is currently high in the ethical and political agenda of many countries. The point that must be discussed is not only reserved for biologists – by whom they were discovered and presented to the general attention – but also other medical professions such as ethicists, media, government, and politicians. The reasons for this are: these super cells have a magic clinical potential in tissue repair and they represent the future relief of a wide range of incurable diseases, or replacement of defective organs and tissues, by restoring their normal functions.

With all its contraversiality, due to its origin, the question is: can these cells be isolated and used? If so, under what conditions and restrictions

In order to discuss the moral aspect of isolation and use of HuSC, it is essential that we first understand exactly what these cells are, where they come from, their intended application, and the ethical questions regarding its different sources.

What Are Stem Cells? Many years of work on the origin of blood cells led to the concept of Hematopoeitic Stem Cells (HSC) that could serve as progenitors for all blood cell types. The concept of a similar multipotent bone marrow stem cell for connective tissues was first presented by Owen (15). Stem cells are unspecialized cells that can self-renew indefinitely and differentiate into more mature cells with specialized functions.

Where Do They Come from? Stem cells originate from different sources (early embryonic stages, embryos, some fetal tissues, the umbilical cord and several adult organs such as the bone marrow).

Until recently, it had been widely assumed that embryonic stem cells were the only pluripotent stem cells capable of differentiating into cells of ectodermal, mesodermal, and endodermal origin. In contrast, adult stem cells localized in different tissues were thought to be specific to that tissue (16). Recently, it has been reported (in animal models) that adult HSC are not limited to form only blood cells, but can differentiate

into many other cells types such as hepatocytes, cardiocytes and myocytes (17, 18). It is now clear that beside embryo and fetal tissues, adult bone marrow contains endothelial stem cells and a rare population of mesenchymal progenitor cells (MSC) as first described by Friedenstein (19).

At the beginning, cord blood was used as a main source of stem cells for transplantation to replace bone marrow. With the advent of new technique and facilities for culturing and cultivating stem cells, today many laboratory and institutes are working with embryonic and fetal stem cells as well as mesenchymal stem cells as their source of clinical use.

This new way of treatment opened up a new horizon in medical practice and research, allowing for replacement therapies that could prove as the way of the future, making certain incurable ailments treatable. They could also compensate for the shortage of organ tissues.

HuSC may eventually be cryopreserved, allowing both clinicians and researchers easy access to well defined cell line populations. These cells could then be differentiated on demand to form specific organ tissues. Of course along with this therapeutic potential come complex ethical issues related to cell origins. As mentioned before, there are three sources of HSCs: preimplantaion human embryos, cadaveric human fetal tissues, and adult human stem cells. The two first have been active areas for ethical debates for decades. There are, even to this day, serious ethical questions regarding embryonic stem cell usage, because we have to sacrifice a viable organ which could effect the donor of this embryo, and although the use of these cells are somehow permitted, controversies persist. Therefore we should be on the look out for alternative sources, like the adult stem cell. The very positive point of using adult stem cells is their relatively little ethical problems compared to other potential sources, because they can be easily harvested from autologous or allogenic donors.

Limitation of adult stem cells in bone marrow is the main reason why they are not used in previous studies. The second reason was the difficulties associated with growth in culture. Recently, efforts to grow mesenchymal stem cells obtained from bone marrow in culture conditions showed successful results. This is good news for clinicians meaning to practice with less ethical questions burdening them.

Within the last two years we developed and used new techniques to culture and differentiate MSC from different sources (bone marrow, cord blood, peripheral blood) (20). As can be seen in figures 1 to 3, we were only able to grow, differentiate and harvest MSC from bone marrow cultures, which gave us enough differentiated cells to be clinically applicable. In contrast to some investigators, we did not succeed with the two other sources. Erics et al (21) claimed this could be due to the culture media and conditions of different laboratories. We concluded that MSC from cord blood and peripheral blood do not proliferate in our culture conditions. However, 100% of our Bone marrow samples yielded MSC. We have reported bone marrow to be the best source of MSC (21) for both research and cell or gene therapy, and with less ethical complications. How useful will they be in therapy? Some studies show hopeful signs. Among these are our first trials with autologous MSC transplant in myocardial infarcted and Multiple Sclerosis patients who have displayed encouraging signs to this point (Mohyeddin et al. unpublished data) (22).

Figure 1. Homogenous monolayer of BM MSC culture

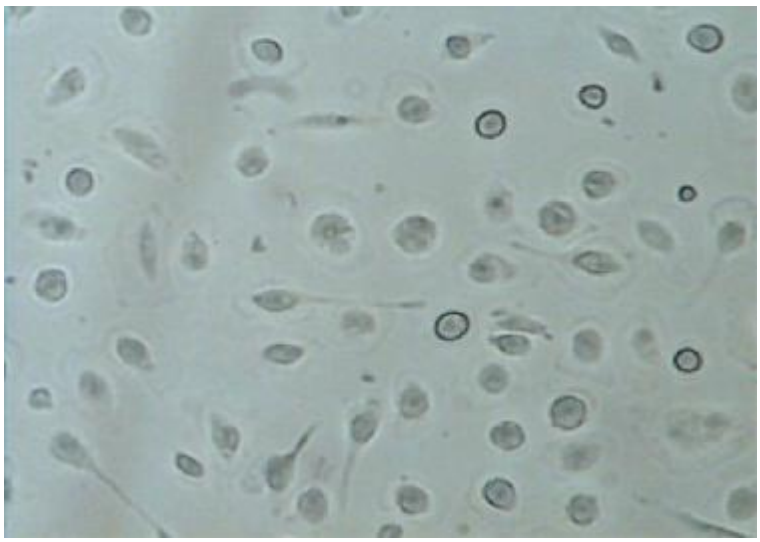

Figure 2. Heterogeneous cells of CB culture

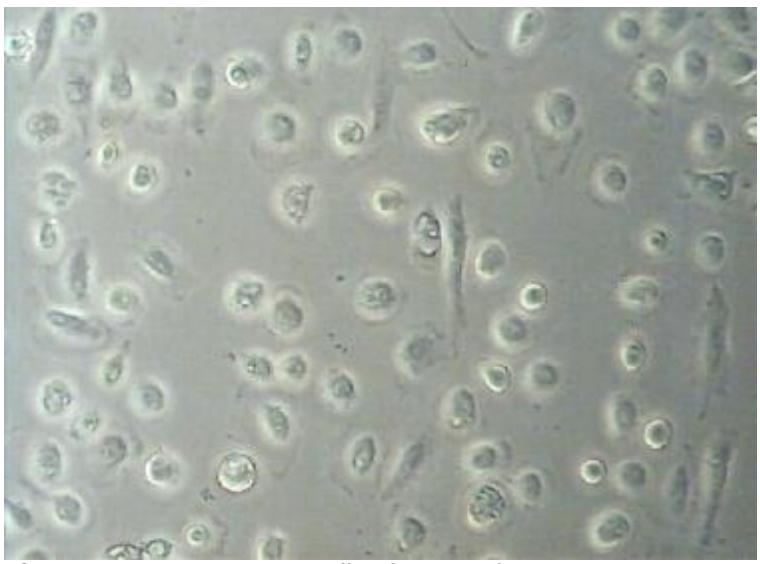

Figure 3. Heterogeneous cells of mPB culture

CONCLUSION

We must not neglect to mention the most recent ethical focus concerning these magic cells, that being the potential tumorigenecity of these cells. There are reports that stem cells turn into cell lines can themselves transform to tumor cell lines and be the actual source of cancer development. A recent report is a piercing danger signal warning us to be aware of the consequences, and give the society the rightful knowledge so they know what they will be exposed to with this novel therapeutic agenda (23).
It seems, like all other issues, we must first consider all the potentials, all the risks, and all the possibilities before we do anything, because nothing comes to us without a degree of risk.

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