The Role of Preservation in Transplantation*

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Introduction

Let us look first into the advantages and disadvantages of preservation in clinical transplantation. I should mention that we are talking of short-term preservation up to 72 hours, rather than preservation for indefinite periods of time. The latter will have to wait until problems of freezing and thawing have been solved, but this still appears to be something for the distant future. What, then, are the advantages?

First, it minimizes the total anoxia time. Although it is well known that human cadaver kidneys can maintain viability up to ten hours by simple hypothermia, it is our feeling that this is not good enough. In cadaver kidneys, the organ is already damaged during the agonal period of the donor, and the additional cold storage time undoubtedly further damages the organ, perhaps permanently. Furthermore, if preservation for more than ten hours is necessary, some method of perfusion is needed.

Second, it allows potential recipients to stay at home either on central dialysis or chronic dialysis until a properly matched kidney becomes available. The patients actually do not have to be called until a matched kidney is known to be present, thus eliminating unnecessary admissions and great disappointments. Furthermore, if the potential recipient cannot be reached immediately, he is still not excluded from receiving that particular kidney. It, of course, allows the total recipient pool to be tremendously increased, because patients who are dialyzed in different centers or in different cities can be selected by computer and can be considered for a transplantation.

Third, adequate preservation allows for histocompatibility testing between the donor and a pool of recipients and the direct cross match between the donor white cells and the best matched recipients.

Fourth, function and damage can be evaluated before the actual transplant, thus eliminating those organs which have been irreversibly damaged during the agonal period of the donor. This aspect is still in the investigational stage, but it appears that the perfusion characteristics are of the greatest importance.

Fifth, adequate preservation is essential for organs such as the liver and heart, because preparation of the recipient is more time-consuming. This problem at the present time is usually eliminated by preservation in the donor, the so-called heart-beating cadaver.

Sixth, it makes the transplant an elective instead of an emergency operation, which can be of the greatest importance if the kidney becomes available during a period of time when all operating rooms are filled.

Seventh, if preservation and selection of organs could be perfected, a much larger source of donor organs would become available. If we are going to be using the so-called neurological deaths only, not enough kidneys will become available to treat all patients in chronic renal failure. However, if we could use kidneys from other patients, such as automobile accident victims or other trauma cases who either enter the emergency room dead on arrival or die within the first 20 minutes, the number of available organs would be tremendously increased.

Finally, it does allow a smaller staff on the transplant team, since the donor nephrectomies, as well as the transplantations, can be done by one team.

Methods

Perhaps at this point we should briefly mention the different methods that have been used for preservation of whole organs. They are hypothermia, hyperbaric oxygen, isolated perfusion, metabolic inhibitors, and, finally, a combination of the above methods. When our studies were initiated, we felt that perfusion would theoretically be the best method, as oxygen could be supplied, and CO_2 and metabolic waste products could be removed. To eliminate the problems of microemboli, we started with an acellular perfusate such as serum or plasma. However, we were plagued initially by the same problems that all other investigators have had with isolated perfusion—increasing perfusion pressure, decreased flow, and tissue edema. On implantation, even after short periods of preservation, the organs did not function; or, if they did function, they showed evidence of some permanent damage.

We then noticed that, if the plasma were frozen and quickly

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thawed, a precipitate developed in the plasma, producing a completely opalescent solution. We found that the most efficient way of removing this precipitate was by serial filtration through Millipore filters, and that, by so doing, a clear solution was obtained. Perfusion with this cryoprecipitated plasma eliminated the problems of rising perfusion pressure and tissue edema. When fat stains were used on the kidneys perfused with normal plasma, multiple fat droplets were seen in the capillaries, the glomeruli and the tubules. Fat stains of kidneys perfused with cryoprecipitated and filtered plasma did not show these fat emboli; thus, it became obvious that the etiology of the rising perfusion pressure was due to fat emboli obstructing the capillary system. When blood is used, these emboli can come from blood cell aggregates; but even if the cellular components are removed, the end stable lipoproteins denature, and their aggregates are just as destructive. Furthermore, this process is self-perpetuating. Once decreased capillary flow is produced, it results in tissue hypoxia, which is shown to produce cellular swelling, especially when combined with hypothermia. The cellular swelling by itself produces increased capillary resistance and further decreased capillary flow, and the cycle continues until death of the cells and the organ results.

Results

We next performed 24-hour and 72-hour preservation studies in dogs, and autotransplantation was combined with immediate contralateral nephrectomy. All animals in both groups survived. The average BUN rise in the 24-hour group was 80 mg%, occurring usually on the third or fourth day, while in the 72-hour group the BUN rose to an average of 140, again on the third or fourth day. However, there was a subsequent rapid decline in the BUN, so that the 24-hour groups had normal BUNs by the seventh or tenth day, while in the 72-hour group the BUN returned to normal by the third week. The animals were then retested after six months, and conventional as well as electronmicroscopy studies revealed normal architecture. Para-aminohippuric acid and inulin clearance studies were within normal limits, and none of the animals developed hypertension. In order to be sure that there was no acceleration in the rejection process, we did several homotransplants using 24-hour perfused kidneys, and the animals rejected their kidneys in the normal period of time ranging from 7 to 21 days.

In August, 1967, we did our first human preservation study; in this, the kidney was preserved for 17 hours. The patient subsequently developed tubular necrosis lasting two weeks, after which the kidney started to open up. His creatinine clearance went as high as 40, at which time he had his first rejection episode. This was partially reversed, but he subsequently had two more rejection episodes requiring maintenance on fairly high doses of steroids. Six months after transplantation he entered the hospital with a ruptured gallbladder secondary to amyloidosis, from which he later succumbed. Of particular interest is the fact that no amyloid was found in the transplanted kidney six months after transplantation.

At that time, our equipment was not transportable, and we found that if the kidney was obtained in one hospital and had to be transferred to the Medical Center before preservation could be started, the anoxia time was still considerable. The preservation unit was thus made transportable, so that it could be moved to the operating room where the donor kidneys were obtained. The perfusion circuit, details of which have been published in several other articles, basically consists of a pulsatile pump, a heat exchanger, an organ chamber, a membrane oxygenator, a cooling system, a pressure recorder and a battery system. For perfusing human kidneys, we use fresh frozen AB+ plasma which is cryoprecipitated immediately before use. The final filter in the Millipore filter system is 0.22μ and acts also as a bacterial filter. Immediately before use, several additives, such as phenolsulfthalein, magnesium, steroids and antibiotics, are added to the perfusate. We have used this method in 42 patients, and the longest period of preservation has been 36 hours. The kidney functioned immediately.

Summary

Although it is too early to draw any definite conclusions from these results, as a period of two years is probably necessary to evaluate cadaver kidney transplantation in humans, it appears that our well-matched patients have much fewer problems than our poorly matched patients. It is hoped that by preservation methods such as those discussed, improved methods of tissue typing, and better immunosuppressive therapy, we will be able to raise the survival level of cadaver kidney transplantations to the level between 80 and 85% presently being obtained in transplantations using living, related donors.