The Use of UW Solution in Clinical Transplantation

A 4-year Experience

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The development of the University of Wisconsin (UW) cold storage solution has extended safe preservation of the liver and pancreas from 6 to 24 hours or more. From May 1987 until November 1991, 288 livers and 163 simultaneous pancreas/kidney transplants were performed using UW solution. The mean preservation times were: liver, 12.7 ± 4.4 hours, pancreas 17.2 ± 4.4 hours, and kidney, 19.2 ± 4.3 hours. Included in this series were 35 reduced-sized liver transplants, 7 cluster transplants, and 132 combined liver/pancreas retrievals. No differences in allograft function or graft-related complications were seen in organs preserved for less than or longer than 12 hours or in grafts from combined liver/pancreas retrievals. All pancreas/kidney transplants and most liver transplants were performed semi-electively. Actuarial 1-month patient and graft survival after liver transplantation was 91.4% and 80.2%, and at 4 years was 74.0% and 62.0%, respectively. After pancreas/kidney transplantation, the actuarial patient survival at 1 month and 4 years was 99.4% and 90.5%, respectively, whereas pancreatic and renal allograft survival at 1 month was 97.5% and 96.8%, and at 4 years was 83.0% and 83.4%, respectively. The ability to extend preservation times with UW solution has many advantages; however, the most important contribution of UW solution to clinical transplantation has been the increased utilization of scarce donor organs for more recipients because the previously imposed constraints on preservation time have been removed.

TWO METHODS OF kidney preservation were introduced in the late 1960s, one using continuous hypothermic pulsatile perfusion[1] and the other using simple cold storage.[2] Both methods have been used clinically for more than 20 years. These methods have allowed an increase in the number of kidneys available for transplantation and have made it possible to perform the transplant as a semi-elective procedure.

The introduction of cyclosporine into clinical transplantation in the early 1980s dramatically improved transplantation results for extrarenal organs such as the liver, pancreas, and heart, and more recently, for the lung. Methods that were successful for kidney preservation, however, were not of equal success for preservation of extrarenal organs. The limit of organ preservation was only 4 to 10 hours, which made organ sharing difficult and required extrarenal transplants to be performed on an emergency basis.

We presented our experimental results in 1986 at the American Society of Transplant Surgeons, using a canine model of pancreas preservation,[3] and demonstrated successful 72-hour preservation using the University of Wisconsin (UW) solution. A year later, at the International Transplant Conference in Pittsburgh, we showed that the liver could be safely preserved for 48 hours[4] and the kidney for 72 hours[5] with the same solution. Additionally, we presented our preliminary results using this solution for clinical liver preservation.

This report details our experience with the UW solution for organ preservation from its clinical introduction in 1987 until November 1991. During this period, we performed 288 liver transplants and 163 pancreas/kidney transplants, using the UW cold storage solution for preservation. Four hundred sixty-four cadaveric kidney transplants also were performed during the same period using continuous hypothermic pulsatile perfusion[6] but those data will not be presented in this article.

Materials and Methods

Liver Transplantation

A total of 288 liver transplants were performed between June 1987 and November 1991. Three hundred thirty-

Presented at the 103rd Annual Scientific session of the Southern Surgical Associations, Hot Springs, Virginia, December 1–5, 1991.

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Accepted for publication December 30, 1991.

TABLE 1. *Indications for Primary Liver Transplantation in Adult Recipients Using UW Solution*

Indication	No. of Patients
Alcoholic cirrhosis	72
Chronic active hepatitis	23
Primary biliary cirrhosis	19
Malignancy	18
Sclerosing cholangitis	17
Cryptogenic cirrhosis	10
Hepatitis B	9
Inborn errors of metabolism	7
Fulminant hepatic failure	4
Other	5
Total	184

five livers were procured by our team. One hundred thirty were retrieved from our procurement area and 138 were from outside our procurement area. Sixty-seven livers were sent to other centers, whereas 20 livers were procured by other teams and sent to our center.

The method of organ retrieval has been described previously.[7] Briefly, after dissection of the liver or liver and pancreas, the aorta was cannulated and UW solution was used for intra-aortic perfusion as well as for *ex vivo* perfusion after the organs were removed. Likewise, the gallbladder and the common bile duct were flushed with UW solution, which is important for preservation of bile duct epithelium.[8] The recipient operation usually began at 8:00 A.M., unless the condition of the recipient was critical, in which case the operation was initiated immediately on return of the retrieval team. All adult patients were transplanted with the use of veno-veno bypass; however, this was not used in pediatric recipients. Indications for liver transplantation in adults are shown in Table 1 and for children in Table 2. The UNOS urgency classification for the adult and pediatric recipients is shown in Table 3. Thirty-five pediatric recipients received a reduced-sized liver: nine right lobes, nineteen left lobes, and seven left lateral segments. A quadruple immunosuppressive protocol was used that included antilymphocyte globulin, OKT3 (Orthoclone; Ortho, Rariton, NJ), azathioprine, prednisone, and cyclosporine, unless the patients were entered in the prospective randomized FK506-cyclosporine trial. The distribution of preservation times for the livers in this series is shown in Figure 1. The mean preservation time was 12.7 ± 4.4 hours.

TABLE 2. *Indications for Primary Liver Transplantation in Pediatric Recipients Using UW Solution*

Indication	No. of Patients
Biliary atresia	37
Cryptogenic cirrhosis	4
Fulminant hepatic failure	4
Chronic active hepatitis	2
Neonatal hepatitis	2
Cystic fibrosis	2
Other	5
Total	56

TABLE 3. *UNOS Status of University of Wisconsin Liver Transplant Recipients 1987–1991*

Status I	Status II	Status III	Status IV
10.2%	19.3%	26.7%	43%

Combined Pancreas/Kidney Transplantation

There have been 163 combined pancreas/kidney transplants performed during the past 4 years. The surgical techniques have been previously described,[9] and all but 10 pancreas transplants (enteric drained) were performed using the bladder drainage technique. Recipients were all juvenile diabetics with end-stage renal failure. The distribution of preservation times for the pancreas are shown in Figure 2. The mean pancreas preservation time was 17.2 ± 4.4 hours and that of the kidney was 19.2 ± 4.3 hours. Almost all recipients returned to the transplant unit after surgery, and only 3% required a short stay in the intensive care unit, primarily because of cardiac instability. Immunosuppression also consisted of quadruple protocol as described above.

Cluster Transplantation

Seven patients received a cluster transplant consisting of the liver, pancreas, and a portion of the duodeum as described by the Pittsburgh group.[10] The average preservation time for the cluster organs was 11.3 hours (range, 6.5–18).

Organization of the Operating Room Schedule

An example of the usual method of scheduling the operating room for multi-organ donor transplants is shown in Table 4. Once a multi-organ donor has been identified, the operating room staff is immediately notified and an operating room is made available at 8:00 A.M. for the liver

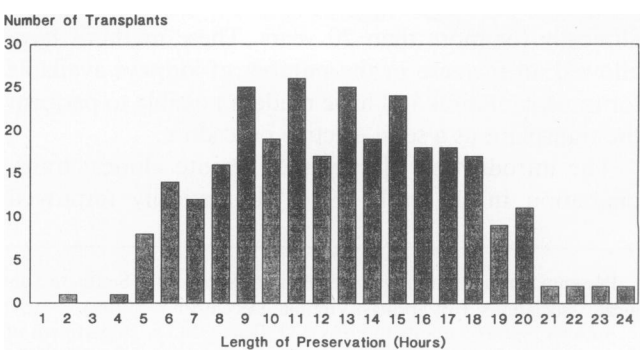

FIG. 1. Distribution of 288 liver transplants preserved with UW cold storage solution.

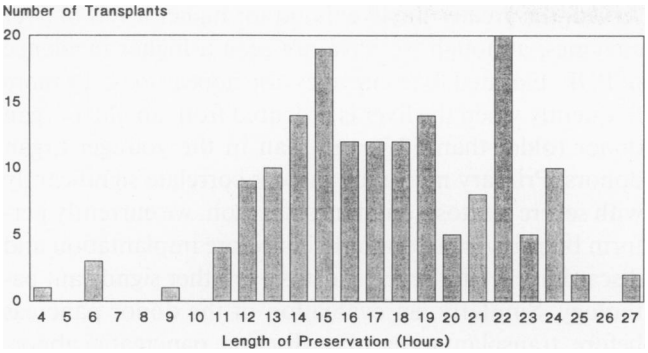

FIG. 2. Distribution of 163 pancreas transplants preserved with UW cold storage solution.

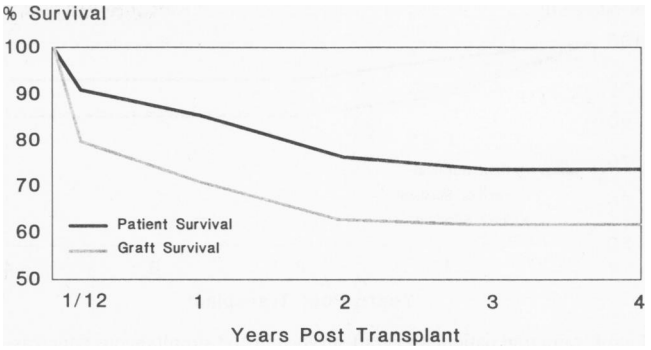

FIG. 3. Actuarial patient and graft survival in 288 liver transplants using UW cold storage solution.

transplant. The pancreas/kidney transplant follows in the next available operating room, and the second kidney from the multi-organ donor is usually transplanted the following morning at 8:00 A.M.

Results

Liver Transplantation

Figure 3 shows the 4-year actuarial patient and graft survival. One-month patient and graft survival was 91.4% and 80.2%, respectively. Patient survival at 1 and 4 years was 86% and 74%, respectively, whereas graft survival was 71% and 62%, respectively. The incidence of primary nonfunction (PNF) was 6.6%; hepatic artery thrombosis, 6.3%; bile duct stricture, 2.4%; and retransplantation was required in 16.0% of the recipients. There were no differences in the rates of PNF, hepatic artery thrombosis, or bile duct stenosis in livers preserved for less than or more than 12 hours. Grafts preserved for less than 6 hours, however, showed less hepatocellular injury, as indicated by lower serum enzymes, including aminotransferases and lactate dehydrogenase, than in livers preserved for 12 hours or more ($p < 0.05$). Before transplantation, livers procured between 1987 and 1990 were analyzed histologically by biopsy, but the transplant was performed, irrespective of the biopsy results. Beginning in January 1990, all liver biopsies that demonstrated severe macrovesicular or microvesicular steatosis were discarded because of the unacceptably high incidence of PNF in these livers.[11] Elimination of these unsuitable livers has reduced the rate of PNF from 9.2% to 4.0% (not significant). The length of stay in the intensive care unit after liver transplantation did not correlate with the length of preservation, but appeared to correlate with the condition of the patient before transplantation. Recipients that were in the poorest condition at the time of receiving a liver transplant had a longer stay in the intensive care unit.

Combined Pancreas/Kidney Transplantation

After combined pancreas/kidney transplantation, there was one initial nonfunction (0.6%) and two episodes of vascular thrombosis (1.2%). There were no episodes of PNF of the kidney, and only three patients required postoperative hemodialysis (1.8%) (Table 5). There was no difference in pancreas or renal allograft function or rate of graft-related complications in organs preserved for less than or longer than 12 hours. Figure 4 shows the 4 year actuarial patient and graft survival in simultaneous pancreas/kidney transplants. The actuarial patient survival at 4 years 1 month was 99.4% and 90.5%, respectively, whereas pancreatic and renal allograft survival at 1 month was 97.5% and 96.8%, and at 4 years was 83.0% and 83.4%, respectively. Because the UW solution is efficacious for all intra-abdominal organs, the results presented in this study include organs from muti-organ donors and included 132 combined pancreas, liver, and renal procurements. There were no differences in graft survival or development of graft-related complications when results with combined (multi-organ) procurements were compared with isolated (individual) organ procurements.

TABLE 4. *Usual Operating Room Schedule for Multiorgan Transplantation: University of Wisconsin Hospital*

Tuesday	Organ retrieval	Afternoon or evening Operating room notified by 7 PM
Wednesday	Liver transplant	8:00 A.M.
	Pancreas + kidney	First available room, usually 2:00–4:00 P.M.
Thursday	Kidney transplant	8:00 A.M. If liver or LRD transplant, first available room

TABLE 5. *Results of Early Pancreatic and Renal Function With UW Solution (n = 163)*

Outcome	No.
Immediate insulin independence	162 (99%)
Primary nonfunction	1 (0.6%)
Vascular thrombosis	2 (1.2%)
Graft pancreatitis	1 (0.6%)
Hemodialysis	3 (1.8%)

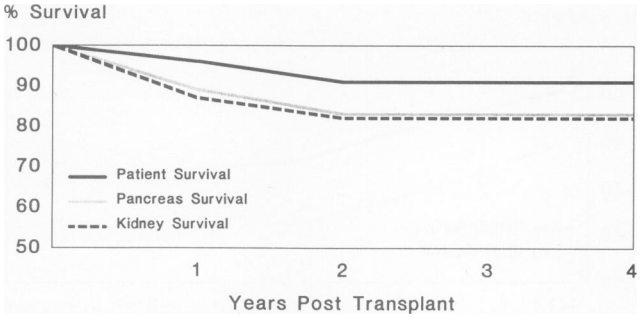

FIG. 4. Actuarial patient and graft survival in 163 simultaneous pancreas–kidney transplants using UW cold storage solution.

Cluster Transplantation

Our experience in cluster operations is summarized in Table 6, which shows the indications for surgery, patient survival, and cause of death. All recipients of a cluster transplant had immediate function of the grafts.

Discussion

During the past 4 years, we have used the UW solution for cold storage preservation of the liver, kidney, and pancreas. This method of preservation has allowed extended periods of preservation without compromising allograft function or increasing the rate of graft complications when compared with shorter periods of preservation. The availability of this solution for organ preservation has facilitated reduced-sized liver transplantation, organ cluster transplantation, and combined procurements of multi-organs with a greater margin of safety than previously achieved with other solutions.

Recently, it has been reported[12,13] that the incidence of PNF and the need for retransplantation in liver transplantation increases with increasing preservation time. Figure 5 depicts the incidence of PNF in our series according to the length of preservation. Although a slight trend of increasing PNF with increasing preservation time was seen, this difference was not statistically significant. We have noted, however, that the longer a liver is preserved, the greater the likelihood for higher levels of liver enzymes, although we have not seen a higher incidence of PNF. Elevated liver enzymes also appear to occur more frequently when the liver is procured from an older organ donor (older than 50 years) than in the younger organ donors. Primary nonfunction does correlate significantly with severe steatosis and for this reason, we currently perform biopsies on all donor livers before implantation and discard livers with severe steatosis or other significant pathology. Similarly, an evaluation of the donor pancreas before transplantation may disclose pancreatic abnormalities (fibrosis or chronic pancreatitis) that are contraindications for pancreas transplantation.

The availability of a method to extend the preservation of all intra-abdominal organs has not only contributed to increased usage of organs, improved logistics of organ sharing, and an opportunity for reduced-sized liver and cluster transplantation, but also can make the transplant a semi-elective procedure. Semi-elective liver and pancreas transplantation has had a tremendous impact on anesthesia, operating room scheduling, and surgical personnel. We do not have anesthesiologists in our institution that are assigned to our transplant program; instead all anesthesia staff are assigned on a rotational basis. Performing the transplants during the daytime hours provides our transplant team with a complete complement of anesthesiologists that might not be available if the operations were performed late at night. Furthermore, the advantage of a daytime, regularly scheduled procedure, impacts significantly on the blood bank, which is fully staffed during the transplant. The surgical team also benefits from the capability of performing a transplant as a semi-elective procedure. The staff, fellows, and residents are, in general, well rested, which is more conducive to a long transplant operation. Additionally, the procurement team can rest between the time of the donor and recipient operations. Scheduling the transplant as a semi-elective procedure allows operating rooms to be used at night for trauma and other truly emergency procedures.

The most important contribution of the UW solution

TABLE 6. *Diagnosis and Outcome of Patients Undergoing a Cluster Transplant*

Patient	Age	Diagnosis	Outcome
1	43 yr	Cholangiocarcinoma with positive regional nodes	Died 21 mo Recurrent disease
2	36 yr	Cholangiocarcinoma with positive regional nodes	Died 11 mo Recurrent disease
3	62 yr	Metastatic carcinoid	Died 19 mo Recurrent disease
4	42 yr	Metastatic gastrinoma	Alive 19 mo
5	57 yr	Metastatic islet cell tumor	Alive 11 mo
6	43 yr	Alcoholic cirrhosis, diabetes, multiple previous surgeries	Died 2 mo Graft *vs.* host disease
7	6 mo	Biliary atresia, diabetes	Alive 2 mo

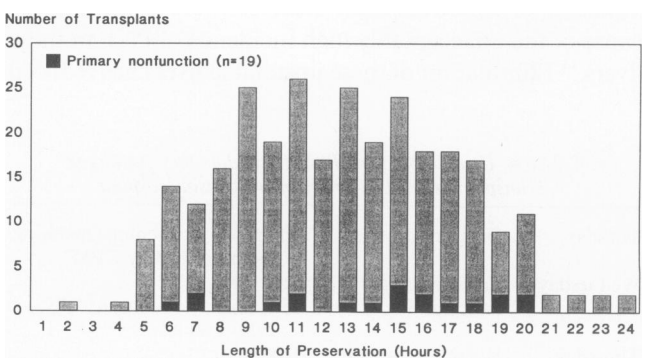

FIG. 5. Incidence of primary nonfunction in 288 liver transplants according to length of preservation.

TABLE 7. *University of Wisconsin OPO Donor Statistics 1986–1990*

Year	No. of Donors	Multiorgan	% Multiorgan	Kidney	Liver	Pancreas	Heart–Lung
1986	70	42	60%	138	10	25	7/0
1987	75	32	43%	142	17	11	16/0
1988	76	50	66%	141	45	23	16/1
1989	72	56	78%	138	51	45	32/2
1990	66	51	77%	120	54	38	22/0
1991*	68	47	69%	118	46	37	23/1

* As of November 12, 1991.

to clinical transplantation has been the capability to increase the use of scarce donor organs, thus increasing the number of patients that can receive a transplant. This is a consequence of the increased preservation time available when this solution is used. Also, recipients can remain at home while awaiting a transplant and have time to arrive at the hospital once an organ is obtained. Recently, several of our liver and pancreas recipients have traveled up to 2000 miles after they have been notified of a potential donor. Previously, patients were required to live in Wisconsin while awaiting a suitable donor organ. A further advantage is that all donors (except possibly older donors) can be considered for multi-organ donation because there is sufficient time before transplantation to examine the organs for suitability for transplantation.

The results in Table 7 show how the use of the UW solution has affected organ procurement in our Organ Procurement Organization. There has been an increase in the number of organs (especially the liver) procured since the introduction of the UW solution at our center. Although there are many problems left to be solved in organ transplantation, the shortage of donor organs continues to be one of the most pressing problems.

From a clinical standpoint, the UW solution has made a significant contribution to organ transplantation at our center as well as at other centers. Undoubtedly there will be improved methods of organ preservation in the future. Although the liver, kidney, and pancreas can be safely preserved for times that currently meet most clinical needs (24 to 40 hours), effective preservation of the heart and lung for similar times has not been consistently obtained. The UW solution may be safe for extended heart preservation (12 to 15 hours) as indicated in some preliminary studies[14,15]; however, a clear demonstration of what is needed to extend heart and lung preservation to 24 or more hours has not been presented.

Potential advantages exist if methods can be developed that extend clinical organ preservation beyond its current limitations. Truly long-term preservation could result in an increase in donor tissue matching, provide an opportunity to prepare a recipient for a particular organ, allow the establishment of organ banks, reduce the incidence of PNF or delayed graft function, and provide an opportunity for immunoalteration of the organ and reduce the incidence of rejection. The accomplishment of these goals will depend on fundamental research that defines the mechanisms of injury to cold-stored organs and provides a list of potentially beneficial therapeutic regimens necessary to suppress the injury.

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