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SUMMARY OF SAFETY AND EFFICACY SUBMITTED IN 1988 TO SUPPORT ORIGINAL 510(k) FILING

Introduction

The Belzer UW Cold Storage Solution preserves organs, by cold storage, just as well as currently marketed media, such as Collins' solution. Belzer UW Cold Storage Solution, hereafter known as BELZER UW-CSS, can be used for cold storage of the liver, pancreas, and kidney. BELZER UW-CSS has the potential to be used as a general solution for most organs, both for initial cooling during in situ donor organ flushing and for subsequent cold storage. Use of BELZER UW-CSS could transform liver and pancreas transplantation from emergency operations to semi-elective procedures.

Preclinical Data

Kidney

Currently, kidneys are preserved by cold storage in Collins' or EuroCollins' solution (ECS) for cold storage transportation for clinical transplantation. Preservation in these solutions is limited to 48 hours. A comparison of EuroCollins' solution to BELZER UW-CSS in a dog transplant model gave 80% survival of dogs receiving kidneys stored for 48 hours in EuroCollins', but no dog survived after organ storage for 72 hours in this solution. In contrast, all dogs transplanted with kidneys preserved in BELZER UW-CSS for 48 to 72 hours survived. Initial post transplant renal function was better in kidneys stored in BELZER UW-CSS, as indicated by serum creatinine values immediately post-transplant and the rapid return of renal function to normal. Thus, storage in BELZER UW-CSS produces less damage to the kidney than storage in ECS. The results of this study indicate the equivalency, and suggest superiority of the BELZER UW-CSS to ECS for kidney preservation.

Clinical Data

Liver

A clinical study compared EuroCollins' Solution (ECS) and the BELZER UW-CSS as preservation and cold storage media for livers harvested for orthotopic transplant. Data for ECS were collected retrospectively, while BELZER UW-CSS data were gathered prospectively. The sample consisted of 126 livers preserved in ECS and 122 livers preserved in BELZER UW-CSS.

Once a donor became available, the liver was isolated and flushed in situ with lactated Ringer's solution and/or ECS solution. The final ex-vivo flush utilized either ECS or BELZER UW-CSS with subsequent storage in the same medium. The preservation time for each liver was recorded. After transplantation, graft function was assessed by the following selected clinical laboratory variables (SGOT, SGPT, alkaline phosphatase, total bilirubin, prothrombin time and partial thromboplastin time) for seven days after surgery and at one month post transplant. Post transplant patient follow up included monitoring for indication of graft dysfunction or rejection, which might indicate the need for a retransplantation. Donor and recipient selection followed the requirements established by the respective institutions sponsoring the transplant procedure.

Two hundred forty-eight liver transplants (126 in ECS group and 122 in the BELZER UW-CSS group) were done in 219 patients. Mean liver preservation times were significantly different for the two treatment groups, with BELZER UW-CSS livers preserved 88% longer than ECS livers (see Table 1).

Table 1

	ECS (n=126)	BELZER UW-CSS (n=122)	
Mean Preservation Time (hours)	5.53±0.14	10.39±0.47	(p<0.01)
Range (hours)	0.75-10.0	0.5-28.7	

The principle differences among the various laboratory values examined between the two treatment groups occurred in SGOT, SGPT, total bilirubin and alkaline phosphatase. Mean levels of SGOT and SGPT in BELZER UW-CSS patients were significantly lower than ECS patients on the first day after surgery.

The differences between the ECS and BELZER UW-CSS groups in total bilirubin and alkaline phosphatase became apparent in the seven-day follow-up period. At the end of seven days, alkaline phosphatase levels in the BELZER UW-CSS patients were significantly lower than those in the ECS patients whereas total bilirubin levels were slightly higher in BELZER UW-CSS patients, than in ECS patients.

The need for retransplantation was higher in the ECS group, compared to the BELZER UW-CSS group (19 vs. 10). There were 23 deaths over 21.5 months for ECS patients compared to seven deaths over four months in the BELZER UW-CSS group. The incidence of hepatic artery thrombosis was greater for ECS patients (7 vs. 3), as well. It should be noted, the observation period for patients in the retrospective (ECS) sample was longer than that for BELZER UW-CSS patients (21.5 vs. 4 months).

In conclusion, BELZER UW-CSS was found to compare favorably with the present preservation cold storage solution, ECS. These data show that the use of BELZER UW-CSS for liver preservation prior to transplant can safely extend storage times. In addition, livers preserved in BELZER UW-CSS solution showed better post transplant function, as evidenced by lower enzyme levels (SGOT, SGPT), when compared to livers preserved with ECS.

A safety concern with the use of both Collins' solution or BELZER UW-CSS relates to the high potassium concentration. Both of these solutions must be flushed from the vascular space of the preserved liver prior to transplantation to prevent a systemic overload of potassium. Therefore, no contraindications to use of this solution are anticipated particularly since this solution is not given to the patient but is flushed from the donor organ prior to transplantation.

Pancreas

A clinical study was performed to compare the effectiveness of ECS and the BELZER UW-CSS as preservation media for cold storage of human pancreas grafts intended for transplant.

ECS data (six grafts) were collected retrospectively while BELZER UW-CSS data (nine grafts) were obtained prospectively. Graft function post transplant was assessed by examining serum and urinary amylase values, as well as blood glucose levels, for seven days following surgery and at one month.

The mean preservation time for pancreas grafts stored in BELZER UW-CSS was significantly longer than for those stored in ECS (Table 2).

Table 2

	ECS n=6	BELZER UW-CSS n=9
Mean Preservation Time (hours)	3.7±0.3	8.7±1.4
Range (hours)	3.0-5.0	4.0-16.0

There were no statistically significant differences in mean Day 1 serum amylase, urinary amylase or blood glucose levels between the two treatment groups, although Day 1 serum amylase values were higher in ECS versus BELZER UW-CSS patients.

Over the seven day postoperative period, serum and urinary amylase levels were not significantly different in the ECS and BELZER UW-CSS groups. However, blood glucose values tended to increase at the end of the week in ECS patients, but decreased in BELZER UW-CSS patients.

In conclusion, these data show that pancreas grafts preserved with BELZER UW-CSS or EC are substantially equivalent when compared by post transplant function.

Summary

Results from clinical trials demonstrate the ability of this solution to safely preserve kidney, liver, and pancreas prior to transplantation. Furthermore, this solution extends the preservation time for all of these organs compared with the duration of organ preservation deemed safe and effective with Collins' solution. This should increase the supply of much needed and valuable donor organs by reducing organ wastage.

Thus, this solution is both safe and substantially equivalent to Collins' and EuroCollins solutions.