Transplant Int (1992) 5: 77–80

TRANSPLANT
International

The use of the University of Wisconsin (UW) and Euro-Collins (EC) solutions either alone or in a combined method*

J. C. García-Valdecasas, F. J. González, L. Grande, A. Rimola, M. Navasa, J. Fuster, A. M. Lacy, E. Cugat, and J. Visa

Department of Surgery, Liver Transplant Unit, Hospital Clínic of Barcelona, Villarroel 170, E-08036 Barcelona, Spain

Received May 2, 1991/Received after revision July 16, 1991/Accepted August 28, 1991

Abstract. From June 1988 to October 1990, a total of 100 orthotopic liver transplantations (OLTs) in 91 patients were performed at the Hospital Clínic of Barcelona. Euro-Collins (EC) solution was used as the flush and storage solution in 29 livers, and the University of Wisconsin (UW) solution was used in 24. A combined method, consisting of flushing and harvesting the liver with UW solution through the portal vein and with EC solution through the aorta, was used in the remaining 47 livers. Livers harvested using such a combined method showed substantially better postoperative function in terms of AST, ALT, and prothrombin activity than those harvested in EC solution alone. Although AST and ALT values were lower in patients whose livers were harvested using the combined method than with UW alone, differences were not significant. On the other hand, prothrombin activity was consistently better in the UW group. Bilirubin levels, platelet count, and bile output showed no difference among the three groups. We conclude that the combined use of UW and EC solutions for flushing and harvesting is not hazardous to human liver preservation and, in fact, may considerably reduce the amount of UW solution needed and, consequently, the costs.

Key words: UW solution, in liver transplantation – Euro-Collins solution, in liver transplantation – Preservation solutions, in liver transplantation

Since 1983, orthotopic liver transplantation (OLT) has become an effective therapeutic modality for end-stage liver disease [10]. Up until 1987, the mainstay of liver preservation was cold storage in Euro-Collins (EC) solution, which provides acceptable graft function within a preservation time of 9 h [3]. The University of Wisconsin (UW) solution subsequently proved to be a major advance in organ harvesting. Its safety and efficacy have been widely demonstrated for extended preservation of the human liver [1, 6–8, 11, 15–18]. Nevertheless, due to its numerous components, the cost of UW solution is generally quite high. Therefore, in June of 1989, we began using UW solution in combination with EC solution. The aim of this study was to retrospectively compare postoperative graft function in livers harvested either in EC solution alone, in UW solution alone, or in a combination of the two solutions.

Materials and methods

From June 1988 to October 1990, a total of 100 OLTs in 91 patients were performed at the Hospital Clínic of Barcelona. EC solution was used as the flush and storage solution in 29 livers and UW solution was used in 24. The remaining 47 livers were harvested using a combined method in which UW solution was flushed through the portal vein and EC solution through the aorta. Table 1 presents data on the graft recipients, including sex, age, and indication for transplantation. Donor groups (EC, UW, and combined) were similar with respect to age, sex, cause of death, length of hospitalization, and liver function (Table 2).

Table 1. Recipient data

Group	EC	UW	Combined	
Total no. of grafts	29	24	47	NS
Mean age ± SE	44.4 ± 11	42 ± 10	43.8 ± 9	NS
Sex (male/female)	16/13	12/12	26/21	NS
Indications for OLT				
1. Fulminant hepatic failure	3	6	6	
2. Cirrhosis				
Chronic active hepatitis	9	1	4	
Cryptogenic	5	6	10	
Alcohol	2	5	9	
3. Cholestatic diseases				
Primary biliary cirrhosis	5	3	9	
Sclerosing cholangitis	1	1	0	
4. Other diseases	3	1	2	
5. Retransplants				
immediate	1	0	2	
late (chronic rejection)	0	1	5	

* Preliminary results from this study were presented at the First International Congress of the Society for Organ Sharing in Rome in June 1991 and will also appear in *Transplantation Proceedings*.

Offprint requests to: J. C. García-Valdecasas

Table 2. Donor data

Group	EC	UW	Combined	*P*
Numbers of donors	29	24	47	
Age (years)	24.8 ± 2	28.4 ± 1	23.3 ± 2	NS
Sex (male/female)	16/13	12/12	25/22	NS
Mean number of days in hospital	3.6 ± 0.5	3.4 ± 0.6	2.4 ± 0.7	NS
Liver function (mean)				
AST	77 ± 11	46 ± 6	80.8 ± 8	NS
ALT	93 ± 34	48.8 ± 8	70 ± 15	NS
Bilirubin (mg/dl)	1.0 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	NS

Table 3. Score for early postoperative graft function

Parameter	Assigned value
Serum alanine aminotransferase (IU/l)[a]	
< 1000	1
1000–2500	2
> 2500	3
Bile output (ml/day)[b]	
> 100	1
40–100	2
< 40	3
Prothrombin activity[c]	
> 60 % (spontaneously)	1
> 60 % (with fresh frozen plasma administration)	2
< 60 % (despite fresh frozen plasma administration)	3

[a] Highest value within the first 72 h after transplantation. Normal values in our laboratory < 40 IU/l
[b] Mean value during the first 72 h after transplantation
[c] Lowest value within the first 72 h after transplantation

Table 4. Early graft function and type of organ harvesting

Group	EC	UW	Combined
Score: I and II (good, intermediate)	20 (69 %)	20 (83 %)	42 (89 %)
Score: III (poor)	9 (31 %)	4 (17 %)	5 (11 %)

Organ procurement

All livers were harvested in a similar fashion with dissection of the porta hepatis and celiac axis. Mobilization of the liver was not performed until the liver was cooled. The liver was perfused with either EC or UW solution through the portal vein and the aorta. In the group using the combined method, two liters of UW solution was flushed through the portal vein, while EC solution was used through the aorta. Around 250 ml was left in the bag for a back table flush through the celiac axis. No precooling was done. All livers were obtained on a multiorgan basis with kidneys in 100 % of the cases, hearts in 60 %, and pancreases in 20 %. Livers were flushed and preserved totally in UW solution when procurement and harvesting were also performed for pancreases or when there were two organ donors.

Recipient operation and perioperative care

The previously described operative technique was used [2, 14]. Hepatic replacement was performed in all cases by the same surgeons. Prior to reperfusion of the liver, the hepatic graft was flushed with HaemoC. Patients were managed in a similar way during the postoperative period, following a previously established protocol. Immunosuppression consisted of azathioprine, cyclosporin A, and steroids (triple therapy).

The following parameters were evaluated in the three groups (EC, UW, and combined): cold ischemia time, immediate graft function in terms of AST, ALT, prothrombin activity, bilirubin, platelet count, and bile output from day 1 to day 7. The probability of graft survival was also calculated, with a maximum follow-up of 12 months. In order to obtain a complete picture, early postoperative graft function was graded using a scoring system previously described [5]. In brief, a score was obtained from the peak ALT value, the mean 24-h bile output, and the lowest prothrombin activity measured during the first 72 h. For each patient the score corresponded to the sum of the assigned value of each parameter, with a possible range from 3 to 9. Depending on their scores, patients were classified into three different groups: I (good early graft function) when the score was 3, or 4, II (intermediate early graft function) when the score was 5 or 6, and III (poor early graft function) when the score was 7–9 (Table 3).

Statistics

Statistical analysis was performed using the analysis of variance factorial and repeated measures. Actuarial survival curves were calculated according to the conditional probability of Kaplan and Meier. Curves were compared by means of the log-rank test. Figures are given in absolute values ± standard error (SE).

Results

Preservation time

The cold storage time, measured from the time of portal venous perfusion until the time of reperfusion in the recipient, once the portal vein anastomosis was completed, had a mean of 253.8 ± 16 min (range 180–430 min) in the EC group while it was 300.7 ± 13 min (range 216–720 min) in the combined group and 539 ± 50 min (range 310–1080 min) in the UW group. There was a significant difference between the UW and the other two groups ($F = 28.137$, $P = 0.0001$).

Postoperative liver function

There was one primary nonfunction in the combined group (preservation using the combined method again). One patient in the UW group was retransplanted after 10 days (this time with a graft preserved using the combined method) because of acute hepatic failure, with a rapid rise in ALT and a sharp decrease in prothrombin activity. Nevertheless, the pathology showed a normal or near-normal pattern of the liver tissue.

Figure 1 shows the AST postoperative levels in the three different groups. As can be seen, livers in the combined group fared better than those in either of the other groups. An analysis of variance (repeated measures) showed an F value of 6.79 ($P = 0.0018$). From day 1 to day 5, differences were significant only between the EC and combined groups (Dunnet $t = 2.2$–3.2, significant at 95 %). UW values were not different from EC or combined group values on any of the postoperative days considered.

Postoperative ALT levels were also consistently better in the combined group (ANOVA $F = 5.973$, $P = 0.0037$). Again, the differences were significant only between the EC and combined groups on postoperative days 1–5. Values in the UW group did not differ from those in either of the other groups on any given day (Fig. 2).

With respect to postoperative prothrombin activity, levels through the 1st week were always better in the UW

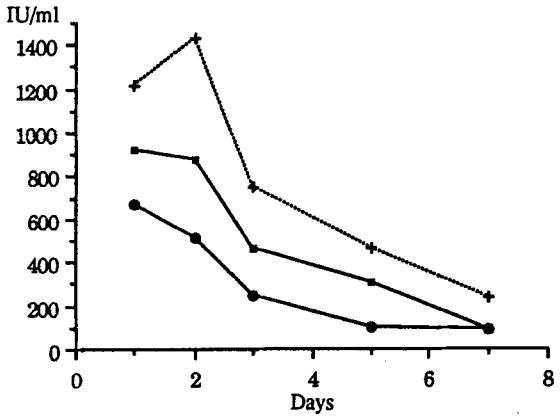

Fig. 1. Immediate postoperative AST levels. The combined group fared better than either of the other groups (ANOVA, $F = 6.79$ $P = 0.0018$). + EC group; ■ UW group; ● combined group

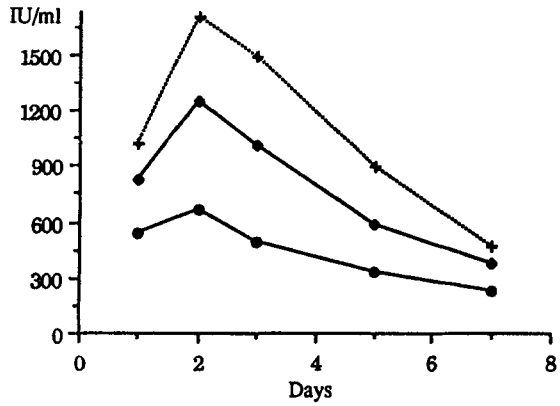

Fig. 2. Immediate postoperative ALT levels. Again, the combined group did better than either of the other groups, but the differences were only significant between the EC and combined groups (ANOVA, $F = 5.97$, $P = 0.0037$). Symbols as in Fig. 1

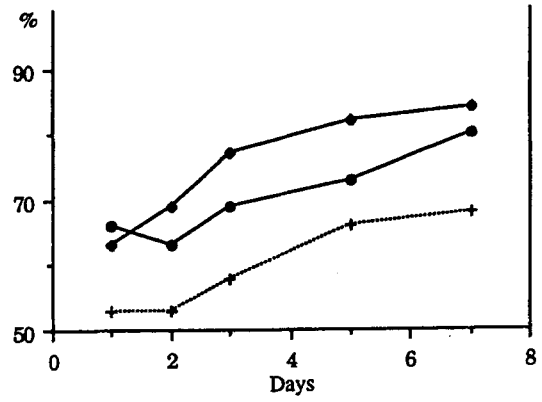

Fig. 3. Immediate postoperative prothrombin activity during the first week was significantly better in the UW group (ANOVA, $F = 10.1$ $P = 0.0001$). Symbols as in Fig. 1

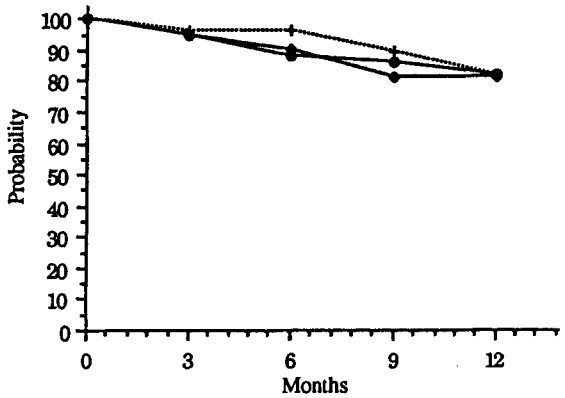

Fig. 4. Actuarial graft survival. At 12 months all groups have a survival probability of 82%. Symbols as in Fig. 1

group (ANOVA $F = 10.1$, $P = 0.0001$). On postoperative days 1 ($F = 3.27$, $P = 0.04$), 2 ($F = 5.1$, $P = 0.008$), and 3 ($F = 7.5$, $P = 0.0009$), either UW or combined was better than EC. On the other hand, on postoperative days 5 and 7 ($F = 8.4$, $P = 0.0005$), only UW values were significantly better than those in the other groups (Fig. 3).

Neither the evaluation of postoperative bilirubin levels ($F = 0.559$, $P = 0.57$) nor the platelet count ($F = 0.827$, $P = 0.44$) nor the bile output ($F = 1.38$, $P = 0.25$) showed any difference among the three groups.

When we considered the score already mentioned for early postoperative liver function, we found that nine (31%) of the EC-harvested livers were in group III (poor early graft function), while only four (17%) in the UW-harvested group and five (11%) in the group using the combined method were. The differences, however, were not significant (Table 4).

Need for retransplantation and graft survival

There was one early retransplantation in each group: in the EC group, due to arterial thrombosis, in the combined group because of primary nonfunction, and in the UW group, due to an unknown cause. A total of six patients were retransplanted in the follow-up period because of chronic rejection: three in the EC group, two in the combined group, and one in the UW group. The probability of graft survival at 12 months in the three groups was very similar, between 80% and 82% (Fig. 4). No deaths during the follow-up period could be related to the type of preservation.

Discussion

Euro-Collins solution has been used as the standard for liver preservation in Europe as well as in the United States, allowing safe cold storage for up to 9 h with subsequent excellent liver function. Since 1987, the University of Wisconsin solution, described by Belzer and his coworkers [1, 7, 8, 11, 15–19], has become the new standard in liver preservation.

Some researchers have suggested that the consequences of combining different solutions for organ flushing and harvesting may be additive and beneficial [4, 13]; others say they may be deleterious [9, 12, 19]. In fact, it has previously been shown that initial flushing with Ringer's lactate or EC solution significantly decreases the survival rate in an experimental rat liver transplant model [19].

This has been related to initially induced severe sinusoidal endothelial damage [9, 12]. However, recently published data [4, 13] using various types of combined methods in human liver transplants do not substantiate this finding.

Although our program has not varied the emergency basis of OLT substantially, we have been able to show that such a combined method, even with long periods of ischemia (up to 720 min), is a safe procedure since, in our series, there was only one primary nonfunction. Although this early failure occurred in the combined group, this gives an overall incidence of 2.1 % (1/47) in this group, which is well within the range of previously published data [4]. The 47 livers harvested this way showed substantially better postoperative liver function in terms of AST, ALT, and prothrombin activity than those in the EC group. On the other hand, when compared to the UW group, AST and ALT values were lower in the combined group; yet, the differences were not significant. It has to be noted that the preservation time, although significantly longer in the UW group (mean 9 h), was within the safe limit for EC-preserved organs. We therefore postulate that the combined method described here is not hazardous to the liver. Moreover, this combined method may considerably reduce the quantity of UW solution needed. The price for a liter in our hospital is currently U.S. $ 200, which brings the total price for the combined group (taking into account the value of 6 liters of EC solution) to U.S. $ 600, whereas it is U.S. $ 1800 for the UW group. In other words, using the combined method reduces the cost by two-thirds.

The tendency towards higher transaminase levels in the UW-harvested livers suggests worse ischemic damage. As has been pointed out by others, ischemic changes are time-dependent, even in UW-preserved livers [4, 15]. Previously, published data has emphasized the safety of extended preservation in UW solution with equally good postoperative liver function [1, 7, 11, 15–18]. Nevertheless, a recent study by Starzl's group [4] showed that the retransplantation rate and the primary nonfunction rate rose as cold ischemia time increased. The results herein suggest that the preservation time should always be kept at a minimum. Aware of the importance of good, immediate postoperative liver function, we are reluctant to change the emergency basis of OLT in our clinical program. However, we are currently working on a prospective and randomized trial to substantiate this fact.

References

1. Belzer FO, Southard JH (1988) Principles of solid-organ preservation by cold storage. Transplantation 45: 673
2. Calne RY (1987) Liver transplantation: the Cambridge/King's College Hospital experience. Grune and Stratton, Orlando, pp 3–540
3. Collins GM, Bravo-Shugarman M, Terasaki PI (1969) Kidney preservation for transportation; initial perfusion and 30 hours' ice storage. Lancet II: 1219–1220
4. Fukurawa H, Todo S, Imvertarza O, Casavilla A, Min Wu Y, Scotti-Foglieni C, Broznick B, Bryant J, Day R, Starzl TE (1991) Effect of cold ischemia time on the early outcome of human hepatic allograft preserved with UW solution. Transplantation 51: 1000–1004
5. Grande L, Rimola A, García-Valdecasas JC, Mas A, Fuster J, Navasa M, Lacy AM, Llach J, Gonzalez FX, Robusté J, Visa J (1991) Primary liver graft nonfunction. Always an indication for retransplantation? Transplantation (in press)
6. Jamieson NV, Lindell S, Sundberg R, Southard JH, Belzer FO (1988) Preservation of the canine liver for 24–48 hours using simple cold storage with UW solution. Transplantation 46: 517–520
7. Kalayoglu M, Sollinger HW, Stratta RJ, D'Alessandro AM, Hoffman RM, Pirsch JD, Belzer FO (1988) Extended preservation of the liver for clinical transplantation. Lancet I: 617–619
8. Kalayoglu M, Stratta RJ, Sollinger HW, Hoffman RM, D'Alessandro AM, Pirsch JD, Belzer FO (1989) Clinical results in liver transplantation using UW solution for extended preservation. Transplant Proc 21: 1342–1343
9. McKeown CMB, Edwards V, Phillips MJ, Harvey PRC, Petrunka CN, Strasberg SM (1988) Sinusoidal lining cell damage: the critical injury in cold preservation of liver allografts in the rat. Transplantation 46: 178–191
10. National Institutes of Health consensus development conference statement: liver transplantation (1984) Hepatology 4 [Suppl]: 107
11. Olthoff KM, Millis JM, Imagawa DK, Nuesse BJ, Derus LJ, Rosenthal JT, Lilewicz AL, Busuttil RW (1990) Comparison of UW solution and Euro-Collins solutions for cold preservation of human liver grafts. Transplantation 49: 284–290
12. Otto G, Wolff H, Uerlings I, Geleert K (1986) Preservation damage in liver transplantation. Influence of rapid cooling. Transplantation 42: 122–124
13. Schwartz ME, Nishizaki T, Thung SN, Manzarbeitia C, Maharajh A, Gordon R, Miller CM (1991) Initial flush solution for donor liver procurement: lactated Ringer's or UW solution? A randomized, prospective trial. Transplant Proc 23: 1554–1556
14. Starzl TE (1969) Experience in hepatic transplantation. Saunders, Philadelphia, pp 1–545
15. Steffen R, Krom RAF, Ferguson D, Ludwig J (1990) Comparison of University of Wisconsin (UW) and Eurocollins (EC) preservation solutions in a rat liver transplant model. Transplant Int 3: 133–136
16. Stratta RJ, Wood RP, Langnas AN, Duckworth RM, Markin RS, Marujo W, Grazi GL, Saito S, Dawidson I, Rikkers LF, Pillen TJ, Shaw BW (1990) The impact of extended preservation on clinical liver transplantation. Transplantation 50: 438–443
17. Todo S, Tzakis A, Starzl TE (1988) Preservations of livers with UW or Euro-Collins solution. Transplantation 46: 925–927
18. Todo S, Nery J, Katsuhiko Y, Podesta L, Gordon RD, Starzl TE (1989) Extended preservation of human livers grafts with UW solution. JAMA 261: 711–714
19. Yu W, Coddington D, Bitter-Suermann (1990) Rat liver preservation. II: Combining UW solution and Eurocollins solution or Ringer's lactate abrogates its protective effect. Transplant Int 3: 238–240