Association Safety of Liver Preservation Solutions at the State University of Campinas From 2010 to 2014

C.H.P. Reigada[a], E.C. de Ataide[a], T.d.A.P. Mattosinho[a], L.B.E. Costa[b], C.A. Escanhoela[b], and I.F.S.F. Boin[a,*]

[a]Unit of Liver Transplantation, State University of Campinas, Brazil; and [b]Department of Anatomical Pathology–State University of Campinas, Brazil

ABSTRACT

The probable reason for mixing solutions during the harvesting procedure is due to the presence of multiple transplant teams that have their own solution usage tradition. Despite numerous studies comparing the efficacy of different preservation solutions, there is no study addressing the associating solution and if there is any impact on liver graft and patient survival. The aim was to evaluate the effect of the association of preservation solutions during the harvesting procedure on liver transplantation outcomes, especially in relation to the degree of preservation injury in the postreperfusion period and patient survival. We analyzed 206 transplants that were distributed as follows: when there was association (89/206 = 43.2%) and when there was no association (117/206 = 56.8%). There was a statistically significant difference in relation to the degree of preservation injury correlated to cold ischemia time ($P = .009$, odds ratio 1.992; 95% confidence interval 1.185–3.347). Severe harvesting (grades III and IV) was 71.8% when the solution was not associated ($P = .008$). There was no difference regarding patient survival either. We found that the association of liver preservation solutions has no impact on patient survival, so it can be done safely. The best survival rate was associated with minimal harvesting.

ORGAN preservation remains an important contributing factor to graft and patient outcomes. During donor organ procurement and transplantation, cellular injury is mitigated using preservation solutions in conjunction with hypothermia. Various preservation solutions and protocols exist with widespread variability among transplant centers [1].

Ischemia-reperfusion injury (IRI) is cellular damage induced by hypoxia, which is exacerbated by the restoration of oxygenation. It involves a process that is dynamic and includes two stages: ischemia and reperfusion.

This concept has been observed in various organs such as heart, kidney, central nervous system, liver, lungs, skeletal muscle system, and bowel. In severe conditions, IRI leads to multiple organ dysfunction and systemic inflammatory response syndrome [2].

Studies have shown that IRI is the leading cause of liver dysfunction and liver failure in the postoperative period. Therefore, improving organ preservation is the key to positively influence liver transplantation outcomes [3–5].

The harvesting procedure is often performed by multiple organ transplantation teams, which leads to the use of more than one type of preservation solution for graft perfusion. This nonuniformity has not been studied in the literature yet, and we do not know the impact on the graft and postoperative outcomes.

The aim was to evaluate the effect of the association of preservation solutions during the harvesting procedure on liver transplantation outcomes, especially in relation to the degree of preservation injury in the postreperfusion period (harvesting lesions) and patient survival.

METHODS

This is a retrospective longitudinal cohort study, carried out in a single center with 231 liver transplantations performed in 206 patients in the Liver Unit of Transplantation–State University of Campinas from 2010 to 2014. Exclusion criteria were patients who underwent standard implantation technique, patients with acute liver

*Address correspondence to Ilka Fatima Santana Ferreira Boin, State University of Campinas, Rua Aldo de Oliveira Barbosa 184, CEP 13086-030 Campinas, SP, Brazil. E-mail: ilkaboin@yahoo.com

0041-1345/17
http://dx.doi.org/10.1016/j.transproceed.2017.01.058

failure, and patients who underwent retransplantation. Variables analyzed were donor age (years), cold and warming ischemia time (minutes), survival time (months), cold ischemia time >8 hours (yes or no), Model for End-stage Liver Disease, red packed blood cells transfused (units), liver profile functions after (international normalized ratio, alanine aminotransferase, and lactate blood levels) measured 24, 72, and 120 hours after reperfusion. The degree of histologic preservation injuries were examined through microscopic analysis of the liver graft after reperfusion. These histologic aspects have been classified according to Leitao et al, such as analyzing degree of steatosis, ballooning and cytoplasmic retraction, necrosis, and hemorrhage (grade I = minimal; II = mild; III = moderate and IV = severe) [6]. These results were distributed into 2 different categories: when there was association of preservation solutions and when association did not occur. In our data, when the solution association concept was applied, 2 different solutions were used for aorta or portal flow such as UW (University of Wisconsin) in the porta cannula and HTK (histidine-tryptophan-ketoglutarate) in the aorta cannula. When only one type of preservation solution was used, it was HTK or IGL-1 (Institut Georges Lopez-1). Patient survival in each group was analyzed using the Kaplan-Meier method, and the Kolmogorov-Smirnov test was applied to continuous variables and χ^2 to categorical variables. Groups were compared according to the harvesting lesions using the log-rank test and regression analyses. The significance level (P) used for all analyses was 5%. The Statistica 11.0 program (2011) (Tulsa, OK, USA) was used to perform the statistical tests.

RESULTS

There was significant statistical difference in relation to the degree of preservation injury and cold ischemia time over 8 hours after comparison between the patients submitted to solution association or not (Table 1), but we observed no difference regarding patient survival (Fig 1). When we analyzed the survival patient rate according to histologic harvesting, we observed that mild alterations (grade I or II) had better survival than grade III or IV ($P < .008$). Regression analyses showed that cold ischemia time >8 hours can cause a risk 2 times larger for grade II, III, or IV lesions ($P = .009$; odds ratio 1.992; 95% confidence interval 1.185–3.347).

Table 1. Descriptive Statistics After Liver Preservation Solution Association or Not

	With Solution Association (89/206 = 43.2%)	Without Solution Association (117/206 = 56.8%)
Median age (y)	48 (18–70)	54 (18–69)
Gender male (%)	58/89 (65.1%)	87/117 (74.3%)
Preservation injury* (histologic evaluation)		
Grade I	7.9%	10.2%
Grade II	39.3%	18.0%
Grade III	21.3%	33.3%
Grade IV	31.5%	38.5%
Warm ischemia time (min)	45 (35–70)	40.8 (35–65)
Cold ischemia time*	540 (270–654)	490 (240–600)
MELD	21 (6–44)	22 (7–80)
RPBC (U)	7 (0–33)	5 (0–16)
Donor age (y)	40 (9–57)	40 (14–68)
INR		
24 h	2.19 ± 1.05	2.07 ± 0.79
72 h	1.62 ± 0.52	1.62 ± 0.71
120 h	1.37 ± 0.24	1.58 ± 1.16
Lactate blood levels (mmol/L)		
24 h	3.7 ± 2.7	3.2 ± 2.4
72 h	2.5 ± 2.3	2.2 ± 1.8
120 h	1.6 ± 1.6	1.4 ± 0.8
ALT (IU/L)		
24 h	880 ± 933	1340 ± 4000
72 h	731 ± 818	950 ± 1089
120 h	429 ± 398	600 ± 904

Abbreviations: ALT, alanine aminotransferase; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; RPBC, red packed blood cells.
*$P < .008$ ($\chi^2 = 11.68$).

DISCUSSION

Early efforts to improve patient and graft survival depended on surgical technique, the introduction of immunosuppression, and the best preservation of liver graft during the harvesting procedure and graft transportation. On the preservation issue, a strategy was needed to reduce the use of intracellular substrates and accumulation of harmful toxins during the ischemia period. Hypothermia up to 4°C reduces oxygen consumption, thus minimizing cellular damage. However, hypothermia alone is not capable of proper preservation, and solutions are required to increase cytoprotection and avoid IRI [3].

Preservation solutions differ in composition but share objectives of reducing graft edema, intracellular acidosis, and production of reactive oxygen species. Furthermore, they provide energy substrates for metabolism. A large number of studies investigated the best liver preservation solution [1,2].

Feng et al carried out one of the largest studies comparing UW and HTK; they performed a meta-analysis involving a combined 1,200 patients with no notable difference in 1-year graft or patient survival [4]. However, HTK is cheaper than UW and as a result many transplantation groups have opted for this solution. Magnus et al identified a $422 (USD) savings per patient with the use of HTK over UW [5].

A multicenter European trial involving 214 patients showed that HTK safe and efficacious for use in liver transplantation with a 1-year graft survival of 80%, 1-year patient survival of 83%, and primary graft nonfunction rate of 2.3% [7].

In our study, solution association can be safely used because no difference was observed in variables such as international normalized ratio, alanine aminotransferase, or lactate blood levels profile (measured 24, 72, and 120 hours after liver transplantation) demonstrating hepatic injury when we compared patients submitted to solution association or not. According to De Gasperi et al [8], liver function profiles could be studied in postoperative liver transplantation but the blood lactate profile, probably more than the absolute level, appears to be a useful indicator of the