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A prospective randomized clinical trial of liver preservation using high-sodium versus high-potassium lactobionate/raffinose solution

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Abstract High-sodium as opposed to high-potassium lactobionate/raffinose preservation solution offers potential advantages in improving the quality of liver storage by reducing potassium-induced vasoconstriction and preventing hyperkalaemia on reperfusion. In our study we evaluated in a prospective trial (encompassing 40 consecutive cadaver donor hepatic retrievals and subsequent transplants) the efficacy of a high-sodium formulation versus the standard high-potassium solution. Quality of preservation was assessed by clinical indices of liver function in the intraoperative and early postoperative phases, including measurements of requirements for blood and blood products and potassium, circulating liver enzymes and bilirubin. Frequencies of acute rejection episodes and primary non-function were also recorded. No significant differences were evident in any of the measured parameters. Thus a sodium-based solution can be used for hepatic preservation, advancing the possibility that it may be possible to develop a single storage solution for clinical multi-organ donor operations.

Key words Liver preservation Storage solution · Sodium and potassium content · Clinical hepatic transplantation

Introduction

The formulation of organ preservation solutions has been based on a few unifying assumptions, including the need to prevent cold-induced cell swelling and to minimize loss of intracellular cations, notably potassium, during storage [2]. However, the requirement for high concentrations of potassium may not be essential, as indicated by recent studies in which a solution based on a mixture of lactobionate and raffinose, osmotic agents originally used in experiments described by Southard and Belzer [7] but with a high sodium concentration, has been found to be effective for experimental hepatic preservation [6, 8]. A positive requirement for a high-sodium low-potassium solution has been indicated in experimental lung preservation [10]. Thus, if multi-organ donor retrieval is to be simplified by the use of a single preservation solution, it will be essential to investigate the cation content of the storage solution in the clinical situation. We undertook a prospective randomized trial of a high-sodium versus a high-potassium lactobionate/raffinose solution for liver graft preservation and demonstrated that both formulations are equally effective for the relevant storage period (12–16 h).

Materials and methods

Between March and December 1992 40 consecutive patients who underwent orthotopic liver transplantation (OLT) in the Liver Transplant Unit at the Royal Free Hospital were prospectively randomized into two groups of these 40 patients 20 (10 males, 10 females, median age 46.5 years, range 22–63 years) were transplanted with a liver preserved with lactobionate/raffinose solution with a high concentration of sodium (group I), and 20 (13 males, 7 females, median age 45.5 years, range 5–68 years) received a liver preserved with lactobionate/raffinose solution with a high concentration of potassium (group II). The compositions of both solutions are shown in Table 1.

Livers were harvested from heart-beating cadavers and perfused in vivo through cannulae in the portal vein (2 l) and abdominal aorta (2 l) with ice-cold Baxter's kidney perfusion solution to cool the abdominal organs and wash out blood. After removal of the liver, the portal vein, hepatic artery and bile duct were flushed, respectively, with 1000 ml, 500 ml and 250 ml of either high-sodium or high-potassium preservation solution and stored in ice. At the recipient operation, immediately before blood reperfusion, the liver was perfused via the portal vein with 500 ml of 4.5% human serum albumin solution to remove the preservation solution. Cold ischaemic times were recorded, and the times required to fashion all three venous anastomoses before blood reperfusion were also recorded as an indicator of exposure to ischaemia outside the ice during surgery.

Table 1 Components of lactobionate/raffinose solution with high-sodium (solution 1) and high-potassium (solution 2) formulations (pH adjusted to 7.2)

	Solution 1 (mmol/l)	Solution 2 (mmol/l)
K^+	25	125
Na^+	125	25
Mg^{2+}	5	5
Allopurinol	1	1
Lactobionate	100	100
$H_2PO_4^-$	25	25
SO_4^{2-}	5	5
Raffinose	30	30
Glutathione (reduced)	3	3

The immediate synthetic function of the transplanted livers was assessed by intraoperative requirements for blood and fresh frozen plasma. The occurrence of reperfusion syndrome was defined as a drop in systemic blood pressure of more than 30% from the baseline, which required intervention with fluids and inotropes, in response to release of vascular clamps from the inferior vena cava and the portal vein on transplantation. In the early postoperative period the quality of liver preservation was evaluated by recording the maximum serum levels of bilirubin, aspartate transaminase (AST), alanine transaminase (ALT) and the lowest platelet count within the first 48 h after transplantation. Potassium given intraoperatively and within 24 h postoperatively and the number of histologically confirmed episodes of acute rejection were also recorded. Problems of morbidity and mortality in the early postoperative period (i.e. patient death or retransplantation within the first 7 postoperative days) were also recorded. The Mann-Whitney *U*-test was used for statistical analysis (values are expressed as median and range).

Results

Over the period of 9 months 40 patients were randomized and transplanted with livers preserved with either high-sodium or high-potassium lactobionate/raffinose preservation solution. There were no exclusions from the study and all 40 patients were included in the analyses. Both groups of patients were similar regarding age, sex and indications of OLT. Livers in both groups were exposed to analogous cold and anastomotic ischaemic times (Table 2).

Intraoperative requirements for blood, fresh frozen plasma and maximum levels of bilirubin, AST, ALT and the minimum platelet counts within first 48 h after transplantation were similar in both groups (Table 2). Intraoperative and postoperative requirements for potassium, and the numbers of acute rejection episodes were also similar (Table 2). The responses to revascularization of the livers were identical, with five patients in each group displaying reperfusion syndrome on revascularization. In each of the five cases from the high-sodium

Table 2 Median values and ranges of function tests. No significant differences were found between the groups for any of the parameters

	Group I	GroupII	*P*-value
Cold ischaemic time (min)	704 (382–957)	676 (498–1211)	> 0.05
Venous anastomosis time (min)	50 (35–66)	49 (34–62)	> 0.05
Intraoperative blood requirements (U)	4.5 (2–20)	6 (1–45)	> 0.05
Intraoperative FFP requirements (U)	5 (0–20)	8 (0–80)	> 0.05
Intraoperative K^+ requirements (mmol)	35 (20–110)	22.5 (10–60)	> 0.05
Max bilirubin within 48 h (μmol)	124 (45–256)	112 (30–318)	> 0.05
Max AST within 48 h (U/l)	891 (210–4559)	668 (77–2617)	> 0.05
Max ALT within 48 h (U/l)	518 (121–2768)	429 (50–2214)	> 0.05
Min platelet count within 48 h (× 10/l)	75 (14–254)	60 (16–132)	> 0.05
K^+ requirements within 24 h (mmol)	100 (10–200)	50 (20–200)	> 0.05
Number of acute rejection episodes	2 (0–5)	1 (0–3)	> 0.05
Number with reperfusion syndrome	5/20	5/20	> 0.05

group, the reperfusion syndrome resolved with administration of intravenous fluids and inotropes, but in one of the five cases in the high-potassium group the patient remained unstable and died in the early postoperative phase (see following) displaying a marked pulmonary oedema. This was the only early problem in the high-potassium group. In comparison, in the high-sodium group one patient with preexisting cardiac disease died at 3 days from cardiac failure with an apparently normal graft, while a second patient was retransplanted at 7 days with a thrombosed hepatic artery after an initial good recovery. In no case in either group was there evidence of overt liver dysfunction in the early postoperative period.

Discussion

This is the first prospective study comparing high-sodium and high-potassium lactobionate/raffinose solutions for the preservation of human livers. Only one study has previously analysed the clinical results of transplantation of livers preserved with high-sodium or high-potassium solutions. In this small retrospective series no differences were found in liver function or survival [6]. In our study, the early synthetic functions of transplanted livers, assessed by intraoperative requirements for blood and fresh frozen plasma, were similar in both groups. Postoperative levels of bilirubin, AST and ALT, used as indicators of ischaemic damage to the liver during storage, were also similar. During cold storage solid organs tend to lose intracellular potassium which may later be removed by the albumin flush during the recipient operation and consequently, on revascularization, requirements for potassium may be proportional to this loss as the organ reaccumulates the cation. However, both intraoperative and postoperative requirements for potassium were similar in both groups.

Poor preservation of the transplanted organ may lead to an increased incidence of rejection [5], but again, in our study, the numbers of acute rejection episodes were similar for both groups. Overall, these findings imply that the quality of preservation did not differ between livers preserved with high-sodium solution and those preserved with high-potassium solution. This is at variance with the traditional approach to organ preservation where high concentrations of potassium in "intracellular perfusates" are considered to produce better organ preservation by conservation of cell energy ("unloading" the transmembrane Na^+/K^+ pump by minimizing cation gradients across the cell membrane), by controlling cell swelling and by prevention of adverse effects caused by changes in intracellular homeostasis [2]. However, Collins et al. observed that high-sodium solutions could also conserve tissue adenine nucleotides [1] and Green and Pegg [4] have suggested that the main feature that distinguishes Collins solution from an extracellular solution is the glucose content, not the high potassium concentration. Other authors have suggested that high concentrations of potassium in preservation fluids could be harmful [3]. The proposed mechanisms of the deleterious effect of high potassium in preservation solutions are considered to be vascular spasm and cardiac arrhythmias if the preservation solution is allowed to return into the circulation. The ratio of the concentrations of sodium and potassium can be reversed in perfusates used for liver preservation without harmful effects [6]. On the other hand, studies on survival of livers preserved with high-sodium compared with high-potassium solution in the rat have been unable to determine whether it is the high sodium that is beneficial or the high potassium that is harmful [8, 9].

In conclusion, this study did not show any significant differences between high-sodium and high-potassium lactobionate/raffinose solutions in preservation-related graft damage and the outcome of liver transplantation, and this may assist in the development of a single preservation solution for multi-organ donor retrievals.

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