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Effect of mannitol on postreperfusion syndrome during living donor liver transplant: A randomized clinical trial

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ABSTRACT

Background and aims: Hemodynamic instability during postreperfusion syndrome remains the most significant concern for transplantation teams. Various strategies have been investigated in an attempt to reduce the occurrence of postreperfusion in liver transplantation, including the use of mannitol as a scavenger of free radicals and inflammatory mediators. The study examined mannitol intraoperative antioxidant effect on reperfusion hemodynamic events during living donor liver transplantation (LDLT).

Methodology: This prospective randomized controlled trial divided 60 participants with end-stage liver disease into two groups of 30 participants each. The mannitol group was administered 1 g/kg of mannitol (20%) in a 500-mL labeled bottle (solution A); the control group received the same amount of normal saline (0.9%) in a 500-mL labeled bottle (solution B). The primary outcome was mean arterial pressure (MAP) postreperfusion. Secondary outcomes were recorded after reperfusion: cardiac output (COP), systemic vascular resistance (SVR), the amount of vasopressor administered, central venous pressure (CVP), and urine output (UOP). This study received ethics committee approval (R 42/2022) and was registered at clinicaltrials.gov (NCT05277623).

Results: The MAP parameters were significantly lower in the control group, with MAP<60 mm Hg in 93.3% of the control group versus 40% of the mannitol group ($p < 0.001$). There was a statistically significant difference regarding SVR ($p < 0.001$). Norepinephrine levels were lower for the mannitol group compared with controls ($p = 0.003$). As regards COP, CVP, and UOP there was no statistically significant difference between the two groups.

Conclusion: Mannitol attenuates the postreperfusion syndrome during LDLT.

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Mannitol; reperfusion; living; donor; liver transplantation

1. Introduction

Liver transplantation is currently the best treatment choice for patients with end-stage liver disease [1]). Hemodynamic instability after postreperfusion syndrome (PRS) remains the most serious concern for all transplantation teams. Several articles described PRS as a severe dynamic instability that may manifest with bradycardia, hypotension, decreased systemic vascular resistance with pulmonary hypertension, as well as increased central venous pressure (CVP) [2]. The potential for cor pulmonale should be well monitored during liver transplantation because any sustained and elevated pressure on the right side of the heart will be reflected in graft perfusion, dissection, and drainage.

Based on the pathophysiology of PRS, increased pulmonary vascular resistance and pulmonary hypertension after reperfusion are among the primary causes of hemodynamic instability. The trigger of this pathology is typically the reoxygenation of an ischemic tissue (in this study, the liver graft), which results in tissue injury and activation of inflammatory markers, ultimately leading to an essential immune response [3].

Mannitol is often used to protect the kidneys during major surgeries and to manage increased intracranial pressure and massive trauma for protection against rhabdomyolysis. The mechanism of action is osmotic diuresis, in which mannitol acts as a scavenger of free radicals and inflammatory mediators [4]. In addition, the release of prostaglandins in response to mannitol results in renal vessel vasodilatation, which improves renal blood flow [5].

In this context and based on the simplicity of the intraoperative use of mannitol, this study examined the intraoperative antioxidant effect of mannitol on reperfusion hemodynamic events during living donor liver transplantation (LDLT), as all literature focused on cadaveric donation which is still not established in Egypt, it adds more constraints and different management protocols than published manuscripts about orthotopic transplants.

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2. Methodology

This prospective, randomized, controlled trial was conducted at Ain Shams Center for Organ Transplantation in Cairo, Egypt, between April 2022 and December 2022. This study assessed 60 participants with end-stage liver disease to determine the intraoperative antioxidant effect of mannitol on reperfusion hemodynamic events during LDLT. All participants were older than 18 years. Patients with known allergy to mannitol, renal impairment, and cardiac dysfunction were excluded. Participants were randomized into two groups of 30 participants each. Before liver graft reperfusion, the mannitol group was administered 1 g/kg of mannitol (20%) in a 500-mL labeled bottle (solution A) and the control group received the same amount of normal saline (0.9%) in a 500-mL labeled bottle (solution B) [6]. After administration, an arterial blood gas sample was obtained to adjust calcium concentrations as well as to correct metabolic acidosis if necessary. The researcher was blinded to the bottle content of solutions A and B. After reperfusion, the participants were assessed for hypotension, defined as mean blood pressure<60 mm Hg or MAP that decreased>30% from baseline for at least 1 minute during the first 5 minutes of reperfusion. Norepinephrine was initiated and administered until MAP was ˃60 mm Hg.

This prospective randomized controlled trial was approved by the local ethics committee (approval number R42/2022) and was registered at clinicaltrials.gov (NCT 05277623). A computer-generated list was used to randomly assign patients into two groups. This study was conducted at Ain Shams University Hospitals in Cairo, Egypt, in accordance with Good Clinical Practice as well as with the Declaration of Helsinki. All participants provided written informed consent.

3. Anesthetic protocol

Rapid induction of general anesthesia was accomplished using rocuronium 0.6 mg/kg, propofol 2 mg/kg, and fentanyl 2–4 µg/kg. Anesthesia was maintained through a balanced anesthesia technique compromising a volatile agent (sevoflurane 0.7–1 minimum alveolar concentration) as well as (1–2 µg/kg/hour) fentanyl infusion for intraoperative analgesia. The following intraoperative assessments were performed: electrocardiography, continuous CVP measurement, noninvasive and invasive arterial blood pressure monitoring, capnometry (end-tidal carbon dioxide), and measurements of oxygen saturation, urine output (mL/hour), and pulse pressure variation for fluid responsiveness. During the neo-hepatic phase, a formal hepatic duplex was performed by a blinded operator using a Flex Focus 800 ultrasound system (BK Medical, Burlington, MA, USA) with a 4.3- to 10-MHz probe to assess the hepatic vasculature and velocities in the portal vein, hepatic vein, and hepatic artery.

4. Measurements

The model for end-stage liver disease (MELD) score, patient demographic data, and right-sided systolic pressure of the heart (to exclude preoperative pulmonary hypertension) were recorded preoperatively. Intraoperative measurements were performed for warm ischemia, cold ischemia, anhepatic phase timing, total fluid, and blood products were given. The primary outcome was mean arterial pressure (MAP) after reperfusion. Secondary outcomes were recorded after reperfusion: cardiac output (COP) using a minimally invasive method device LiDCOunity (LiDCO, Orsman Road, London, UK), systemic vascular resistance (SVR), the amount of vasopressor (norepinephrine) administered, CVP, and urine output.

5. Sample

The sample size calculation was considered based on the results of a study by Sahmeddini et al. [7] that reported a relatively large effect size on the comparison of select vascular parameters for the control group, with no statistically significant differences in the same parameters for the mannitol group. However, a statistically significant difference was observed in the total epinephrine dose in micrograms (µg) at the declamping of the portal vein. For the present study, a sample size of 30 cases per group achieves a power of 80% to reach similar conclusions using paired repeated measure analysis of variance in each group and two independent sample t-tests with a value of $p < 0.05$ considered statistically significant. The sample size was then increased by 20% to compensate for study dropouts.

6. Statistical analysis

Data collection, coding, and entry were performed using the statistical software SPSS, version 23 (IBM, Armonk, NY, USA). Quantitative parametric data were displayed as ranges, standard deviations, and means; otherwise, data were displayed as the median and interquartile range. In addition, qualitative variables were expressed as percentages and numbers. For qualitative data, the chi-square test was used to compare groups. Comparison of groups with a parametric distribution as well as quantitative data was made using an independent t-test, whereas two groups with a non-parametric distribution as well as quantitative data were compared

using a Mann – Whitney U test. Moreover, the accepted error margin was set at 5%, and the confidence interval was set at 95%. As a result, the significance level for the p-value was determined at 0.05.

7. Results

Baseline demographic and clinical data for the 60 participants show no significant differences other than increased body mass index in the mannitol group compared with the control group ($p = 0.004$), as shown in Table 1. All patients received standard anesthetic management and monitoring during the reperfusion phase.

Regarding MAP to indicate hemodynamic status as the primary outcome in Table 2, MAP parameters showed a significant decrease in the control group versus the mannitol group ($p < 0.001$), with MAP<60 mm Hg in 28 (93.3%) of controls versus 12 (40%) patients receiving mannitol Figure 1 There was a statistically significant difference as regard SVR with less decrease in the mannitol group ($p < 0.001$). Regarding the use of vasopressors (norepinephrine), patients who receive mannitol had lower norepinephrine doses than controls ($p = 0.003$) as shown in Figure 2, no additional vasopressors (phenylephrine) were used in either group. Other hemodynamic parameters, including COP, CVP, and urine output, showed no difference between groups. Postreperfusion hepatic duplex showed lower portal vein velocity values in the mannitol group compared with the control group ($p = 0.058$), as presented in Table 3.

Table 1. Comparative Demographic and Clinical Data for the Mannitol and Control Groups.

Participant Characteristic		Control Group ($n = 30$)	Mannitol Group ($n = 30$)	Test Value	p Value
Sex (n)	Female	9 (30.0%)	6 (20.0%)	0.800*	0.371
	Male	21 (70.0%)	24 (80.0%)		
Age (years)	Mean ± SD	48.13 ± 12.22	48.59 ± 13.09	−0.137†	0.891
	Range	16–64	18–68		
BMI (kg/m^2)	Mean ± SD	24.12 ± 4.87	27.95 ± 4.90	−3.037†	0.004
	Range	16–40	17.4–37.2		
MELD score	Median (IQR)	13.5 [11–17]	13.5 [11–18]	−0.297≠	0.767
	Range	6–31	6–27		
Anhepatic time (min)	Median (IQR)	77.5 (60–100)	70 (50–90)	−1.186≠	0.236
	Range	40–180	25–240		
RVSP (mm Hg)	Median (IQR)	17.5 [12–25]	22.5 [15–30]	−1.593≠	0.111
	Range	10–35	10–47		
Cold ischemia time (min)	Median (IQR)	45 (35–50)	47.5 (30–95)	−0.825≠	0.409
	Range	18–110	15–240		
Warm ischemia time (min)	Median (IQR)	40 (30–50)	40 (30–50)	−0.392≠	0.695
	Range	25–70	25–130		
Packed red blood cells (units)	Mean±SD	4.20 ± 2.81	3.43 ± 3.87	0.877†	0.384
	Range	0–8	0–16		
Fresh frozen plasma (units)	Mean±SD	3.00 ± 3.43	1.57 ± 2.18	1.931†	0.058
	Range	0–10	0–8		
Cryoprecipitate (units)	Mean±SD	1.53 ± 3.43	1.73 ± 3.63	−0.219†	0.827
	Range	0–12	0–12		
Crystalloid (Ringer acetate) (L)	Mean±SD	2.63 ± 0.49	2.50 ± 0.51	1.034†	0.305
	Range	2–3	2–3		
Albumin 2% (L)	Mean±SD	4.47 ± 0.51	4.57 ± 0.50	−0.766†	0.447
	Range	4–5	4–5		

*Chi-square test; † independent t-test; ≠ Mann–Whitney U test. Non-significant, p > 0.05; significant, p < 0.05; highly significant, p < 0.01.BMI, body mass index; IQR, interquartile range; RVSP, right ventricle systolic pressure.

Table 2. Postreperfusion MAP, Norepinephrine Dose, CVP, and UOP in both groups.

Postreperfusion Variable		Control Group ($n = 30$)	Mannitol Group ($n = 30$)	Test Value	p Value
MAP (mm Hg)	Mean ± SD	50.43 ± 7.13	60.80 ± 8.83	−5.001†	< 0.001
	Range	37–67	43–75		
Norepinephrine dose (μg)	Median (IQR)	1.35 (0.8–2.2)	0.4 (0.4–0.8)	−3.001≠	0.003
	Range	0.4–2.8	0.4–2.4		
COP (L/min)	Mean ± SD	4.84 ± 0.65	5.14 ± 0.63	−1.837†	0.071
	Range	4–6.5	4.2–7		
SVR (dynes.sec.cm^{-5})	Mean ± SD	768.00 ± 76.93	856.20 ± 83.95	−4.243†	< 0.001
	Range	616–880	713–1020		
CVP (mm Hg)	Median (IQR)	7 [6–9]	6 [4–7]	−1.794≠	0.073
	Range	1–12	0–13		
UOP (mL/hr)	Median (IQR)	100 (50–150)	100 (50–150)	−0.436≠	0.662
	Range	20–200	25–200		

†Independent t-test; ≠ Mann–Whitney U test. Non-significant, p > 0.05; significant, p < 0.05; highly significant, p < 0.01.CVP, central venous pressure; IQR, interquartile range; MAP, mean arterial pressure; COP, cardiac output; SVR; systemic vascular resistance; UOP, urine output.

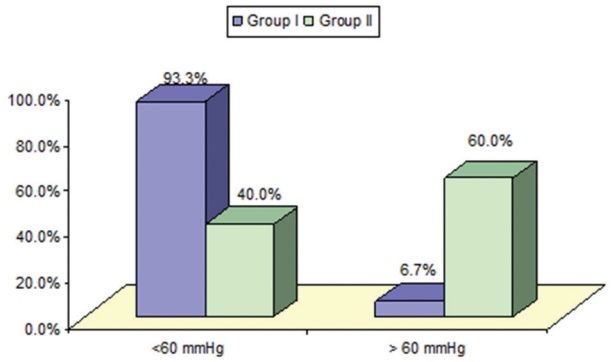

Figure 1. Mean arterial pressure postreperfusion in the control group (Group I) and mannitol group (Group II).

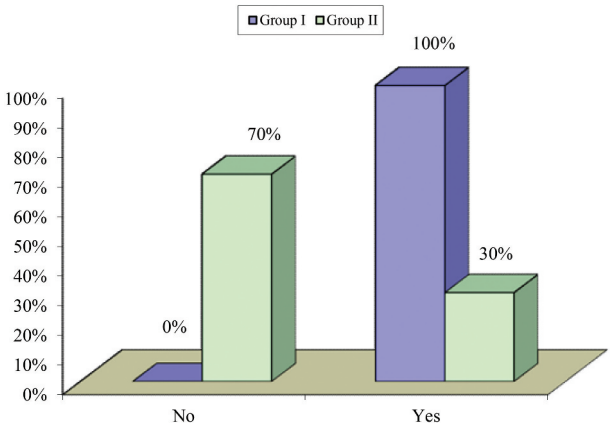

Figure 2. Patients who received norepinephrine at reperfusion in the control group (Group I) and mannitol group (Group II).

8. Discussion

The risk factors associated with PRS must be determined, particularly in cases of elevated risk for aggressive hemodynamic collapse, such as LDLT, in which cardiovascular instability occurs and PRS is usually unexpected, as reported in the literature [8,9,10,11]. The main concern for anesthesiologists is to anticipate and prevent the occurrence of complications, including the following: electrolyte disorders, hypothermia, hyperkalemia [11] the quantity of blood transfused [9] prolonged cold ischemic time without portal shunt [8] not applicable for LDLT, extensive liver and kidney disease [12] as well as left ventricular diastolic dysfunction [13].

Several measures have been studied to reduce the postreperfusion events during liver transplantation, ranging from the use of venovenous bypass [14] liver graft flush and various surgical techniques [15,16,17] and graft-preserving solutions [18,19,20]. However, to date, no specific technique has been proven to prevent the occurrence of PRS events in liver transplantation.

To ensure hemodynamic stability during liver transplant anesthesia, most anesthesiologists tend to choose norepinephrine, as a frequently used active cardiovascular medication in clinical anesthesia. Exogenous norepinephrine administration is necessary to support circulatory failure in critically ill patients. In contrast to these short-term advantages, however, chronic adrenergic stress is harmful to the cardiovascular system [21]. Animal studies indicate that mannitol is characterized by hydroxyl radical scavenging, in addition to its osmotic diuretic effect [22]. Mannitol suppresses spontaneous aggregation of human platelets if exposed to anoxic and reoxygenated conditions in vitro [23], in addition to reducing the production of hydrogen peroxide in patients scheduled for coronary artery bypass graft surgery [24]. Mannitol has also been shown to provide neuroprotection by preventing both cellular necrosis and apoptosis after transient cerebral ischemia [25]. Furthermore, it prevents reperfusion injury that may occur to the ischemic muscle [26] while inhibiting lung harm caused by hepatic reperfusion [27]. In the current study, the use of mannitol decreased hypotension in the postreperfusion period and decreased the use of vasopressors (norepinephrine). Consequently, mannitol infusion may effectively mitigate PRS.

Dembo et al. [6] demonstrated that the patients who received mannitol needed less vasopressor support compared with a placebo group to sustain MAP during orthotopic liver transplantation. In another study on renal transplantation, mannitol that was administered just before removing the vascular clamps decreased the need for post-transplant dialysis, but this approach did not enhance long-term graft performance if inadequate hydration was present [28]. For patients in a different study of mannitol administration during the anhepatic phase, infusion at a rate of 1 g/kg effectively decreased the incidence of PRS without concern for hyponatremia or hyperkalemia [7].

Table 3. Portal Vein Velocity, Hepatic Artery Resistive Index, and Hepatic Vein Flow at Reperfusion.

Reperfusion Variable		Control Group (n = 30)	Mannitol Group (n = 30)	Test Value	p Value
Portal vein velocity (cm/sec)	Mean ± SD	83.00 ± 29.23	68.77 ± 27.84	1.931˙	0.058
	Range	25–150	15–123		
Hepatic artery resistive index	Mean ± SD	0.64 ± 0.07	0.63 ± 0.07	0.631˙	0.531
	Range	0.5–0.8	0.53–0.84		
Hepatic vein flow	Triphasic	29 (96.7%)	27 (90.0%)	1.071*	0.301*
	Biphasic	1 (3.3%)	3 (10.0%)		

*Chi-square test; ˙independent t-test. Non-significant, p > 0.05; significant, p < 0.05; highly significant, p < 0.01.

A limitation of the current study is that it is a single-center study, which limits the generalization of the results regarding liver resection from living donors.

9. Conclusion

In patients with end-stage liver disease who undergo LDLT, administration of intraoperative mannitol reduced reperfusion hemodynamic events in PRS. Further studies are needed to validate the current study results.

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