

Intraoperative Mannitol Does Not Prevent Renal Failure in Orthotopic Liver Transplantation

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ABSTRACT

Objective: To undertake a prospective randomised controlled study to investigate whether there is any beneficial renal effect in the perioperative administration of mannitol in patients undergoing orthotopic liver transplantation.

Methods: Patients presenting in end-stage liver failure for orthotopic liver transplantation had their preoperative renal function assessed by 24 hour urinary creatinine clearance. In a randomised double-blind study they were allocated to receive either mannitol 0.5 g/kg intravenously, or an equivalent volume of 0.9% saline, after induction. All patients had central venous, peripheral and pulmonary artery catheters inserted and received intravenous fluids, blood and blood products based on central pressure measurements, thromboelastographic monitoring, and blood biochemistry. All patients also received intravenous dopamine 2.5 - 3.0 µg/kg/min. Intravenous fluids and urine production were recorded intraoperatively and for the first 24 hours in intensive care.

Results: Twenty five patients were enrolled, 13 in the control group and 12 in the mannitol group. There was no significant difference in the preoperative creatinine clearances (control group 72.1 ± 24.5 mL/min; mannitol group 65.1 ± 33 mL/min, $p = 0.45$), total intraoperative fluid requirements (control group $10,741 \pm 4517$ mL; mannitol group $13,852 \pm 11,827$ mL, $p = 0.38$) or intraoperative urine production (control group 1323 ± 1419 mL; mannitol group 912 ± 493 mL, $p = 0.35$).

Conclusions: We conclude that intraoperative mannitol does not help preserve renal function in the patient undergoing liver transplantation. (*Critical Care and Resuscitation* 2001; 3: 75-80)

Key words: Diuretics, mannitol, dopamine, jaundice, renal failure, liver transplantation

Mannitol is an inert osmotic diuretic that is freely filtered at the glomerulus with minimal absorption in the renal tubule. For over 30 years it has been used prophylactically in the jaundiced patient to produce a diuresis with the aim of preventing renal failure. Its use in this situation continues to be recommended in standard textbooks of anaesthesia and surgery.¹⁻⁵ However, the use of mannitol may itself lead to a large osmolar clearance, resulting in intracellular dehydration

and plasma expansion,⁶ with a reduced haematocrit, red cell volume and plasma viscosity.⁷

The diuresis produced by the osmotic inhibition of water movement in the proximal tubule⁸ and the resultant reduction in the sodium gradient in the ascending limb of the loop of Henle, depends on the state of hydration. The associated plasma expansion increases glomerular filtration rate (GFR) by increasing nephron flow and reducing oncotic pressure.⁹

A retrospective analysis of our liver transplant patients, some of whom had not received mannitol, showed that patients who had not received mannitol had postoperative creatinine clearances that were no different from those who had received it, but that intravenous fluid requirements and urine outputs were significantly greater in the mannitol group.

We undertook a randomised prospective controlled study to investigate whether there is any beneficial effect with the intraoperative administration of mannitol in the patient undergoing orthotopic liver transplantation.

MATERIALS AND METHODS

This study was approved by the Medical Ethics Committee and consecutive patients presenting for orthotopic liver transplantation (OLT) consented to be included in the study. As part of their preoperative assessment, the serum bilirubin and urea, and creatinine clearance from a 24 hr urine sample were recorded. Patients under 16 years of age or those requiring artificial renal support were excluded from the study.

Following induction of anaesthesia, patients were allocated by random number assignment, to receive either 0.5 g/kg of 10% mannitol or an equivalent volume of 0.9% saline intravenously over 15 - 20 minutes. The anaesthetist was blinded to the type of fluid being administered. All patients received an intravenous infusion of dopamine, at 2.5 - 3.0 $\mu\text{g}/\text{kg}/\text{min}$, and were monitored with arterial, central venous, pulmonary artery and urinary catheters. Intra- and postoperative fluid replacement was given as clinically indicated, as were other diuretics. Hourly recordings were made of urine output and intravenous fluid requirements intraoperatively, together with the urine output and intravenous fluid requirements for the first 24 hr postoperatively. The creatinine clearance for the first 24 hr postoperatively was also measured.

The two groups were compared for age, sex and disease aetiology. Statistical analysis using the unpaired t-test compared preoperative serum bilirubin and urea, anhepatic times, pre- and postoperative 24 hr creatinine clearances, and intra- and postoperative intravenous fluids and urine output.

The data are presented as means \pm SD and p value. A value of $p < 0.05$ was considered significant.

RESULTS

There were thirteen patients in the control and twelve in the mannitol group, with the male/female ratio being 10/3 and 9/3 respectively. The average age was 45 years in the control and 51 years in the mannitol group, and the mean anhepatic times were 57 (± 10.3) and 65 (± 18) minutes respectively ($p = 0.19$). Two patients in

the mannitol group and one in the control group required venovenous bypass. The data are presented in table 1.

The intra- and post- operative fluid requirements, urine production and pre- and postoperative 24 hr creatinine clearances were compared. There was no significant difference in the preoperative creatinine clearances (control group 72.1 ± 24.5 mL/min; mannitol group 65.1 ± 33 mL/min, $p = 0.45$), total intraoperative fluid requirements (control group $10,741 \pm 4517$ mL; mannitol group $13,852 \pm 11,827$ mL, $p = 0.38$) or intraoperative urine production (control group 1323 ± 1419 mL; mannitol group 912 ± 493 mL, $p = 0.35$).

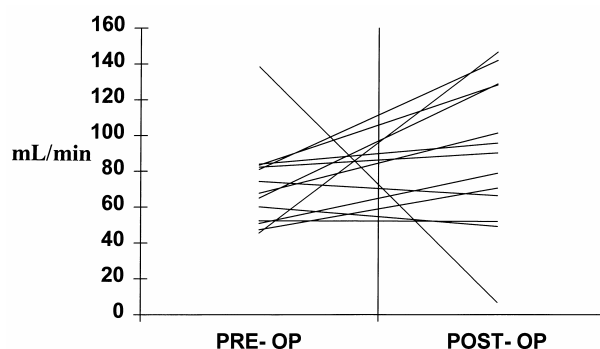


Figure 1. Change in creatinine clearance from preoperative to postoperative value in the control group.

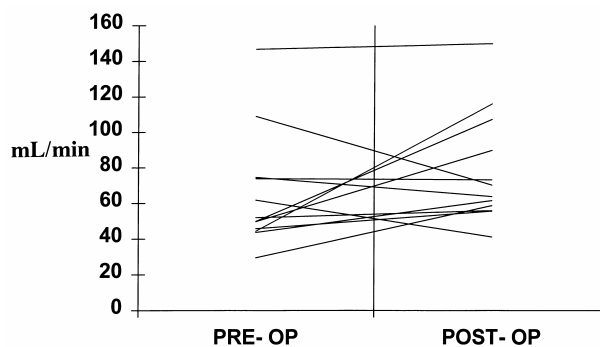


Figure 2. Change in creatinine clearance from preoperative to postoperative value in the mannitol group.

In contrast to our pilot study, there were no differences in postoperative fluid requirements in the first 24 hr (control group $9,670 \pm 7704$ mL, and mannitol group $10,099 \pm 9,827$ mL, $p = 0.90$) or urine production (control group $2,522 \pm 940$ mL and mannitol group $2,338 \pm 1295$ mL, $p = 0.5$). Twenty four hour creatinine clearances were also similar in the two groups (control group 89 ± 41 mL/min and mannitol group 78.6 ± 31.4 mL/min, $p = 0.49$). Pre- and postoperative changes in creatinine clearance in the control group and

Table 1. Preoperative and postoperative changes in creatinine clearance, bilirubin, urea and fluid balance in the control and mannitol groups

Control	Preop bilirubin (µmol/L)	Preop urea (mmol/L)	Preop CrCl (mL/min)	Intraop fluids (mL)	Intraop urine (mL)	24 hr fluids (mL)	24 hr urine (mL)	24 hr post-op CrCl (mL/min)
1	12	5.6	60.0	13500	367	5107	2175	49.0
2	136	4.8	138.3	7440	369	4841	1862	6.7
3	146	3.4	82.2	6800	2618	3102	2680	90.1
4	63	3.6	50.7	8790	390	9300	1483	78.8
5	108	4.9	74.2	16110	381	14500	1683	66.2
6	432	9.3	67.6	6780	620	7400	2888	101.3
7	25	5.6	83.4	3100	804	6700	4490	128.2
8	26	4.7	71.6	10600	410	4798	2902	128.7
9	75	3.6	52.3	13500	665	5030	2101	51.9
10	52	4.1	47.2	9680	1395	8700	2528	70.4
11	58	2.1	81	10390	1600	10029	1913	141.8
12	15	6.3	83.9	20315	2265	32600	3440	95.6
13	90	3.7	45.4	12634	5310	13600	4219	146.5
Mean	95	4.7	72.1	10741	1323	9670	2522	89
SD	110	1.8	24.5	4517	1419	7704	940	41
Mannitol								
1	7	7.7	49.7	4100	770	4100	1780	89.9
2	522	24.2	29.4	11230	373	40300	3000	58.8
3	29	5.3	74.7	6790	480	6550	2433	63.8
4	30	7.1	73.9	8990	1105	8900	1410	73.2
5	32	3.7	146.7	13830	1810	5034	3340	149.8
6	40	3.4	49.8	20600	990	3475	2746	107.3
7	222	5.5	45.8	17000	1300	8514	1040	55.6
8	38	5.1	43.6	6038	290	9500	1111	61.5
9	48	4.2	52.0	10200	1373	10500	5712	55.9
10	24	8.0	44.4	11410	520	8467	1385	116.0
11	102	7.7	61.8	48340	1420	10700	1975	41.1
12	134	7.6	109.0	7690	510	5149	2120	70.3
Mean	102	7.5	65.1	13852	912	10099	2338	78.6
SD	146	5.5	33.0	11827	493	9827	1295	31.4

Preop = preoperative, Intraop = intraoperative, post-op = postoperative, CrCl = creatinine clearance,

in the mannitol group are illustrated in Figures 1 and 2, respectively.

DISCUSSION

It was recognised as early as 1911¹⁰ and later in 1956¹¹ that postoperative deaths were greater in patients with jaundice and that over half of the deaths were due to renal failure. It was also realised however that this may have been contributed to by preoperative dehydration, circulating volume depletion and subsequent intraoperative hypotension.

Dawson demonstrated that in dogs, renal artery clamping or induced haemorrhage caused respectively, a higher death rate and a reduction in renal function, in those that were jaundiced.^{12,13} Both of these outcomes could be prevented by the prior administration of mannitol.^{12,13} Wendling *et al*,¹⁴ however, in a similar experiment in hypotensive dogs, doubted that the

mannitol diuresis necessarily indicated an improvement in renal circulation. Dawson also showed that in human subjects, those with jaundice were at greater risk of dying when compared to non-jaundiced patients. Death was more likely the deeper the jaundice,¹⁵ and jaundiced patients suffered a greater fall in creatinine clearance compared with non-jaundiced patients when having similar types of surgery and that this could be prevented by giving mannitol.¹⁶

Bilirubin has been shown to be a metabolic poison, by uncoupling oxidative phosphorylation¹⁷ and by inhibition of oxygen utilisation¹⁸. Elevated conjugated bilirubin reduces myocardial performance in dogs, possibly contributing to the hypotension and renal failure¹⁹.

Smith,²⁰ in 1967, recommended giving mannitol to patients who had received incompatible blood transfusions, following major trauma, were jaundiced or had

impaired renal function at the time of their operation, in the hope of preserving renal function.

Patients having abdominal aortic aneurysms resected fared poorly if they were not given mannitol²¹ and dogs subjected to infra-aortic occlusion were protected from renal cortical ischaemia if given mannitol,²² whereas elective surgical patients not having aneurysm repair had renal function maintained by intravenous hydration only.²¹ Prospective human studies seemed to confirm that mannitol helped to maintain renal function following cadaveric renal transplants²³ and after operations in patients with obstructive jaundice. Despite these prophylactic measures there was still a percentage who went on to develop established renal failure, these being patients with more severe levels of jaundice or with sepsis present.^{24,25} In contrast, Gubern *et al*,²⁶ showed that giving mannitol made no difference to post-operative renal function in patients having surgery with obstructive jaundice, that it did not improve the renal function in those already impaired, and was ineffective if used when the patient was already dehydrated. The state of hydration was also identified as being important in renal transplantation,²³ and a review in 1986 maintained there was no convincing evidence that mannitol prevented or diminished renal failure if it was of ischaemic origin.²⁷

When mannitol is administered during resuscitation to patients with Swan-Ganz catheters, glomerular filtration rate (GFR) is increased proportionally more than cardiac index suggesting an effect on both GFR and tubular reabsorption. In myoglobin-induced renal failure, where mannitol was thought to have a role in preventing oxidant-induced renal damage, it did not have any cytoprotective effects, or increase renal blood flow. Its main action was due to its diuretic effect, increasing urine flow and preventing intrarenal haem trapping.²⁸

Endotoxin has been implicated in contributing to renal failure in obstructive jaundice.²⁹ Rats injected with endotoxin had a higher death rate associated with renal dysfunction^{30,31} and renal fibrin deposition, suggesting that intravascular coagulation may have been responsible.³¹ Various treatment strategies have been tried to alter the endotoxin-induced mechanism such as indomethacin (to decrease thromboxane production and alter prostaglandin balance in favour of the vasodilator prostacyclin),³¹ polymixin B³² and lactulose,³³ all with favourable results. Paradoxically indomethacin has been shown to decrease renal blood flow and GFR in dogs³⁴ whilst it improved vascular responsiveness to nor-adrenaline in rabbits.³⁵

Animal experiments have suggested that the presence of conjugated bilirubin may be important in reducing the risk of endotoxaemia.³⁶ Endotoxin (detect-

ed by the Limulus assay) was present in the portal blood of patients with obstructive jaundice associated with deeper levels of jaundice. These patients had a significant fall in their postoperative creatinine clearances compared with non-jaundiced patients, and mannitol did not prevent this.³⁷ The bile salt sodium taurocholate has been shown to prevent endotoxin absorption in animals³⁷ but it failed to preserve renal function in postoperative jaundiced patients.³⁸ Sodium deoxycholate administration in humans however led to a significant reduction in post-operative endotoxaemia and renal failure. Mannitol made no difference.³⁸⁻⁴⁰

Liver transplant recipients may have elevated levels of either the conjugated or the unconjugated forms of bilirubin depending on their primary disease. Mannitol and dopamine, either together or separately, have been used in an attempt to preserve renal function in these patients. In a retrospective review,⁴¹ mannitol alone led to more renal impairment than when it was combined with low dose dopamine, and the use of venovenous bypass made no difference. In one study, dopamine without mannitol preserved renal function whether the patients had bypass or not.⁴² The converse has been shown, with dopamine adding no benefit when all patients received mannitol and most had venovenous bypass.⁴³ Irrespective of surgical technique *i.e.* venovenous bypass or "piggy back" operation (preservation of the inferior vena cava) 38% of patients developed renal failure after OLT, with a 50% mortality at 30 days despite the intraoperative administration of dopamine and mannitol.⁴⁴ In another study, there was a 27% postoperative renal failure rate when neither dopamine or mannitol were infused and the post-operative course was uneventful.⁴⁵

The possibility of renal failure occurring postoperatively in the patient with jaundice or liver disease is recognised. Many strategies have been applied in an attempt to improve the outcome in this group of patients, including the use of antibiotics, bile salts, diuretics and veno-venous bypass. We have shown that in the patient presenting for orthotopic liver transplantation, the use of mannitol does not confer any benefit over monitored, adequate, fluid resuscitation.

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