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Title

Sodium bicarbonate infusion in patients undergoing orthotopic liver transplantation: a single centre randomized controlled pilot trial

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The authors declare no conflicts of interest.

Abstract Page

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4. Abstract:

Background: Liver transplantation-associated acute kidney injury carries significant morbidity and mortality. We hypothesized that sodium bicarbonate would reduce the incidence and/or severity of liver transplantation-associated AKI.

Methods: In this double-blinded pilot RCT, adult patients undergoing orthotopic liver transplantation were randomized to an infusion of either 8.4% sodium bicarbonate (0.5 mEq/kg/hr for the first hour; 0.15 mEq/kg/hr until completion of surgery); (n = 30) or 0.9% sodium chloride (n = 30). Primary outcome: AKI within the first 48-hours postoperatively.

Results: There were no significant differences between the two treatment groups with regard to baseline characteristics, MELD and APACHE II scores, and pre-transplantation renal function. Intraoperative factors were similar for duration of surgery, blood product requirements, crystalloid and colloid volumes infused and requirements for vasoactive therapy. Eleven patients (37%) in the bicarbonate group and 10 patients (33%) in the sodium chloride group developed a postoperative AKI (p =0.79). Bicarbonate infusion attenuated the degree of immediate post-operative metabolic acidosis; however, this effect dissipated by 48 hours. There were no significant differences in ventilation hours, ICU or hospital length of stay, or mortality.

Conclusions: The intra-operative infusion of sodium bicarbonate did not decrease the incidence of AKI in patients following orthotopic liver transplantation.

5. Key words: liver transplantation, bicarbonate, kidney injury

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Introduction

The aetiology of liver transplant-associated AKI is multifactorial with risk factors including pre-existing chronic renal dysfunction, diabetes mellitus, long graft ischaemia time, intraoperative massive transfusion, and the nephrotoxic side effects of immuno-suppressants (1-5). Acute kidney injury (AKI) has been reported to occur in 17-95% of liver transplant recipients (6). In this setting renal replacement therapy is required in 5-35% of patients (6). Whilst the long-term consequences of liver transplant-associated AKI are not well understood, the development of AKI is associated with prolonged length of ICU, increased morbidity and a morality of 2-21% (7-9). AKI also imposes a significant pharmacoeconomic burden on health care resources, particularly if renal replacement therapy is required. In this setting mortality has been reported as high as 50% (9). The development of chronic kidney injury post-orthotopic liver transplantation is not only important with respect to the need for long-term renal replacement therapy and renal transplantation, but also increases the patients cardiovascular risk dramatically (10). This clearly emphasizes the need to better identify at-risk recipients and to develop new strategies to prevent or minimize AKI after liver transplantation (11).

Previous studies have suggested that an infusion of sodium bicarbonate might help prevent contrast-induced nephropathy and AKI following cardiac surgery (12-15). However, in the context of cardiac surgery there is current evidence suggesting that intravenous bicarbonate not only fails to prevent AKI (16-19), but also may be associated with an increased mortality (17). Considering these inconsistent effects, and even potential harms, together with the fact that to date no study has investigated the effects of sodium bicarbonate on renal function in the context of liver transplant-associated AKI, we conducted a phase II double-blind

randomized controlled pilot trial to test the hypothesis that an intraoperative infusion of sodium bicarbonate would reduce the incidence of AKI in patients undergoing OLT.

Materials and Methods

The Austin Health Research and Ethics Committee approved this study (number: 4377/2011) and all patients gave written informed consent. We registered the study with the Australian New Zealand Clinical Trials Registry (number: 12612000022864). Between November 2010 and June 2013, we conducted this trial at a high-volume liver transplant centre, in Melbourne Australia. Currently our institution performs approximately 80 liver transplants annually, with over 1000 successful transplants to date. Participants were identified from the liver transplant waiting lists. Inclusion criteria were adults (age > 18 years) and need for primary OLT. Exclusion criteria included preoperative renal replacement therapy, requirement for intraoperative continuous venous-venous hemofiltration (CVVH), hepatorenal syndrome, combined liver-kidney transplant, fulminant hepatic failure, history of congestive cardiac failure, preoperative hypernatremia (serum sodium > 150 $mmol.L^{-1}$), preoperative hyponatremia (serum sodium < 130 $mmol.L^{-1}$), preoperative hypokalemia (serum potassium < 3.0 $mmol.L^{-1}$), end stage renal disease (serum creatinine >300 $mmol.L^{-1}$), and pregnancy.

Patients were randomized to receive an intraoperative infusion of either sodium bicarbonate 8.4% (SB group) or sodium chloride 0.9% (NS group) using a computer-based randomisation program. The trial drug infusion was commenced immediately after induction of anesthesia and before surgical incision, at a dose of 0.5 mEq/kg/hr IV for the first hour, and then at a dose of 0.15 mEq/kg/hr IV until completion of surgery at time of skin closure. As there is lack of uniformity in the dose and duration of therapy with bicarbonate for renal protection among the different clinical trials published, we based our dosing regime on following premise; the majority of the studies evaluating the reno-protective effects of bicarbonate in the context of contrast nephropathy have administered bicarbonate for 6 hours (12,13). Given that accumulating trials in cardiac surgery reported that a 24-hour infusion showed no benefit (14-19), and might increase mortality (17), we considered an intraoperative infusion to be pragmatic, rational and feasible, given that the average duration of liver transplantation in our institution is between 8-12 hours. The infusion was delivered via a central venous catheter using a computerised volumetric infusion syringe. All perioperative clinicians including

anesthesiologists, surgeons and nursing staff were blinded to the trial fluid intervention. Hospital pharmacy staff provided the solutions in identical unmarked blinded syringes. Treatment allocation was only revealed after data analysis had been performed.

Standardization of care

Induction of anesthesia consisted of balanced technique using fentanyl (2.5 ug.Kg^{-1}), propofol (1-2 ug.Kg^{-1}) and rocuronium (1 mg.Kg^{-1}). Vascular access for volume resuscitation consisted of bilateral 8.5 French Arrow RIC® lines (Rapid Infuser Catheters) (Arrow International, Erding, Germany), each connected to a Fluid Management System (Haemonetics Corporation, Braintree, MA, USA). Continuous invasive haemodynamic monitoring included right femoral and left radial arterial lines, a four-lumen central venous catheter, and pulmonary artery catheter with continuous cardiac output and mixed venous saturation measurements (CCO Combo, Edward Life sciences, Irvine, CA, USA). Anesthesia was maintained with 1 minimum anesthesia concentration isoflurane in a 50% air-oxygen mixture, with continuous cistracurium (0.1 mg.kg.hr^{-1}) and fentanyl (1.5 mg.kg.hr^{-1}) infusions.

In-theatre laboratory facilities allowed analyses of electrolytes, glucose, hematology, and arterial blood gases. Thrombelastography® (Haemoscope Corp., Morton Grove, IL) permitted point of care assessment of the quality of hemostasis and rationale use of blood and blood related products. Bloods were sampled at the beginning of each phase and at hourly intervals. Critical bleeding and massive transfusion was in accordance with Australian blood patient management guidelines (20). All crystalloid fluid intervention was with Plasma-lyte 148® (Baxter, Toongabbie, NSW, Australia) and all colloid intervention was with 20% albumin (Albumex 20%, CSL Behring, Australia). Electrolyte disturbances e.g. hyperkalaemia, hypocalcemia, hyperglycemia etc., were managed as per standard medical practice. Bicarbonate was not used to treat acid base derangements in any patients.

All patients underwent a Makuuchi surgical incision and a conventional “piggyback” technique employed. During the pre-anhepatic phase, a restrictive fluid therapy protocol (low mean central venous pressure less than 8 mm.Hg^{-1}) was applied to minimize blood loss. The cava was left in continuity and the hepatic veins were divided within the substance of the

liver, allowing creation of a common patch of the hepatic veins for a wide anastomosis. Pre-anhepatic phase extended until the portal vessels were clamped. Once anhepatic all patients received methylprednisolone (1.5 $mg.kg^{-1}$). Partial occlusion of the vena cava allowed venous return to the heart, and veno-veno bypass was not used in any patient. We used judicious volume loading prior to clamping or partial clamping of the vena cava (mean central venous pressure ~10 $mm.Hg^{-1}$), however once partially clamped we avoided aggressive fluid intervention except to replace on-going blood loss. As cirrhotic patients have increased blood volumes and cardiac output, we tolerated 15-20% blood loss with little volume intervention or vasoactive support, provided mean arterial pressure was greater than 70 $mm.Hg^{-1}$ and cardiac index above 2.0 $L.min.m^{-2}$. Noradrenalin was the vasoactive drugs used in all cases to maintain mean arterial pressure pressures within 20% of baselines values. During caval anastomosis, the donor liver was flushed with 2 litres of Saline 0.9%. Neohepatic phase was managed with noradrenalin for vasoplegia. We used vasopressin and methylene blue for refractory vasoplegia and managed electrolyte abnormalities and reperfusion arrhythmias conventionally. In the setting of cardiovascular instability, or in select patients with significant cardiovascular risks, we used transesophageal echocardiography to guide fluid and vasoactive pharmacological therapy. After completion of surgery, all patients were transferred to the intensive care unit for on-going monitoring and postoperative care, and were extubated according to standardised ICU protocols.

As serum creatinine within the context of RIFLE consensus definitions is widely validated across numerous patient cohorts as a powerful and prognostic metric for defining AKI (21), our primary trial endpoint was the development of liver transplantation-associated AKI, defined as an increase in creatinine greater than 50% from baseline to peak value within the first 48-hours postoperatively, or urine output less than 0.5 $ml.kg.hour^{-1}$ for six consecutive hours (RIFLE Class ‘R’). Other endpoints included changes in acid-base status, duration of intensive care unit (ICU) and hospital stay, adverse events, and hospital mortality. Any complication coded by the hospital’s health information database was cross-checked with the medical records and observation charts for accuracy. Complications were recorded as unexpected events occurring during surgery or the postoperative period, and graded according to the Clavien-Dindo Classification (22). Adverse Events were classified according to the Common Terminology Criteria for Adverse Events (23). Finally, given the potential for

confounding by dilution of serum creatinine (given the large intraoperative fluid requirements) we measured Cystatin C as an additional metric of kidney function.

All clinical chemistry was measured and interpreted at 37°C (alpha-stat). Creatinine, estimated glomerular filtration rate (eGFR), magnesium, phosphate, and liver function tests were measured with a Cobas® 600 analyser (Roche Diagnostics, Switzerland), using a standardised photometric module, linear and non-linear multi-points, and a 2-point calibration. Serum sodium, chloride, potassium, magnesium, ionised calcium, phosphate, albumin, lactate were measured at baseline, at the end of surgery and on postoperative days 1 and 2. Measurement of pH, CO_2, lactate and routine electrolytes in arterial blood was completed on an ABL 800 Flex Blood Gas Analyser (Radiometer, Copenhagen, Denmark) with a fully automated micromode eliminating risk of user-induced bias or loss of accuracy with very small samples, and an interference-protected lactate analyses. The machine calculates the bicarbonate concentration using the Henderson-Hasselbalch equation and the standard base excess (SBE) using the Van Slyke equation, which used reference points: pH = 7.40, pCO_2 = 5.33 kPa and T = 37°C to determine changes in bicarbonate, protein anion and phosphate concentrations and therefore SBE (24). Analysis of the acid base outcomes were performed using Stewart's theory (25), modified to account for the effect of weak acids.

The effective strong ion difference (eSID) was determined using the strong ion concentrations from blood gas results as follows:

Effective SID, $mEq.L^{-1} = [Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [Lactate]$.

To account for the effect of weak acids, albumin and phosphate effects were calculated as follows:

Albumin anions, $mEq.L^{-1}$ = [albumin] x (0.123 X pH-0.631); and

Phosphate anions, $mEq.L^{-1}$ = [phosphate] x (0.309 X pH-0.469).

Strong ion gap (SIG) was then calculated using the following equation:

SIG, $mEq.L^{-1} = [Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] – [Cl^-] – [Lactate] – [Bicarbonate] – [Albumin anions] – [Phosphate anions]$.

Based on a pilot audit from our institutional liver transplant database over a 2-year period, we observed an incidence of AKI of 55% (RIFLE class criteria) within the first 48 hours postoperatively. For this pilot study, we considered a 25% reduction in the incidence AKI between the intervention group and control group to be clinically important. With an alpha level of 0.05 and beta value of 0.8, a total of 29 participants were required in each group. To allow for participant dropout, a total of 60 participants were recruited. All data were analyzed according to the intention-to-treat principle. Continuous data were tested for normal distribution using the D'Agostino-Pearson omnibus test. Between-group comparisons for continuous data were performed with the use of Student's t test or the Mann-Whitney U test and for categorical data with the use of Fisher's exact test or chi-square test for trend where appropriate. All tests were two-tailed and we considered a *p* value <0.05 to indicate statistical significance. Values were reported as mean and standard deviation (SD) and mean difference, or medians with interquartile ranges or odds ratio with 95% confidence interval estimate as appropriate. Data analyses were performed using GraphPad Prism version 6.0 (GraphPad Software, La Jolla California). The study was reported according to the CONSORT guidelines for randomized trials (26).

Results

Sixty-nine patients consented for the study. Nine patients were excluded as they did not fulfil inclusion criteria at the time of surgery, six due to requirement for intraoperative CVVH, two due to presenting with fulminant liver failure, and one due to surgery cancellation (graft mismatch). For the final analysis, 60 participants were included. All patients received the designated trial fluid and there were no breaches in the study protocol. Thirty participants were randomised to the SB group and 30 participants to the NS group.

There were no significant differences between the two treatment groups with regard to baseline characteristics, comorbidities, MELD and APACHE II scores, pre-transplantation

renal function, serum Cystatin C, liver function, hematological and coagulation profiles (Table 1). Intraoperative factors were also similar for the two groups including duration of surgery, blood product requirements, crystalloid and colloid volumes infused, urine output and requirements for vasoactive therapy (Table 2). One patient from the Bicarbonate group and two patients from the Saline group were administered 100 mls of additional sodium bicarbonate (8.4%) for severe hyperkalemia and arrhythmias present on reperfusion.

Immediately postoperatively, compared to normal saline, sodium bicarbonate infusion attenuated the degree of metabolic acidosis with a higher postoperative mean pH ($p=0.001$), mean plasma bicarbonate ($p<0.001$), mean base excess ($p<0.01$), lower mean plasma chloride ($p=0.01$), and mean strong ion gap ($p=0.01$) levels (Table 3). However, there were no statistical differences in these values at 48 hours postoperatively. The key primary and secondary outcome measures are summarised in Table 4. For the primary endpoint, 11 patients (37%) in the SB group and 10 patients (33%) in the NS group developed AKI within the first 48 hours postoperatively ($p=1.0$). There were no differences between the groups in serum creatinine, eGFR, and Cystatin C levels. There were no significant differences between the treatment groups in duration of requirements for renal replacement therapy, ventilatory or inotropic support, or length of ICU stay. Rates of specific adverse events were not significantly different between treatment groups. Length of overall hospital stay was also similar across both groups, and there were no in-hospital mortalities.

Discussion

In this single centre blinded randomised phase II pilot trial, we found that the intraoperative infusion of sodium bicarbonate significantly affected acid-base status during surgery and attenuated immediate post-operative acidosis. However, bicarbonate infusion did not decrease the incidence of early post-operative acute kidney injury (AKI). Supporting this finding there were no significant differences observed between the groups in serum creatinine, eGFR and serum cystatin over the first 48-hours postoperatively. In addition, there were no significant differences in ventilation hours, ICU or hospital length of stay, morbidity or mortality.

Earlier studies suggested that sodium bicarbonate reduced the risk of AKI in the setting of cardiac surgery and contrast induced nephropathy (12-14). Proposed mechanisms for the nephro-protective effects of sodium bicarbonate included urinary alkalinisation and the attenuation of the Haber-Weiss reaction responsible for the formation of harmful renal reactive oxygen species, scavenging of hydroxyl radicals and peroxynitrite from the blood (27-29). Bicarbonate also reduces the rate of intratubular injury from hydroxyl radicals and can prevent hemoglobin-associated pigment nephropathy by reducing the conversion of hemoglobin to met-hemoglobin (30,31). The potential benefit of bicarbonate was initially supported by the findings of a large meta-analysis suggesting that sodium bicarbonate-based hydration prevented contrast-induced nephropathy (32). A more recent meta-analyses by Zapata-Chica and colleagues included 22 studies (5,686 patients) and found that bicarbonate was not superior to 0.9% saline solution for preventing contrast-induced nephropathy in patients with risk factors, nor was it better than saline in reducing the need for renal replacement therapy or mortality (33). Similarly, a recent double-blinded randomized controlled trial showed that sodium bicarbonate infusion was not associated with the prevention of AKI in patients undergoing cardiac surgery, with the authors suggesting that bicarbonate may actually be harmful and adversely affect patient mortality (17). In another other meta-analyses that included five RCT's (1079 patients), bicarbonate did not reduce the incidence of cardiac surgery associated-AKI, and use of bicarbonate prolonged the duration of ventilation and ICU length of stay, and increased the risk of alkalemia (34). The authors advocated that bicarbonate should not be recommended for the prevention of cardiac surgery associated-AKI and perioperative bicarbonate infusions should be administrated with caution. These findings have since been confirmed in similar studies (35,36).

However, other studies have reported that bicarbonate has a reno-protective effect. An individual patient data meta-analysis suggested bicarbonate infusion improves renal outcomes in patients undergoing coronary artery bypass surgery (15). In another recent prospective observational study involving 342 patients undergoing CPB (37), 174 patients that received a perioperative bicarbonate infusion had a lower incidence (35.6 vs. 50%) of AKI compared to patients who did not receive the infusion. The authors reported that low-risk cardiac patients particularly benefited from the preventive treatment with sodium

bicarbonate, while there was no statistically significant difference in the high-risk patient cohort.

In our study, the administration of sodium bicarbonate resulted in normal base excess immediately after surgery, whilst patients in the saline group developed a mild metabolic acidosis. The mechanism of this acidosis is likely a result of significant hyperchloremia in the saline group, a finding well reported in the literature. In animal models of acidosis, sodium bicarbonate may not predictably raise the arterial pH (38,39), a finding also observed in our study. Furthermore, the changes in base deficit seen immediately after surgery were no longer apparent at 24 hours postoperatively. Lastly, sodium bicarbonate administration can result in metabolic reactions that may themselves alter the SID, concentration of weak acids, or $PaCO_2$ (40) or augment the production of lactic acid (41,42) by a shift in the oxyhemoglobin-saturation relationship, enhanced anerobic glycolysis, and changes in hepatic blood flow or lactate uptake (40,43).

Although controversial, sodium bicarbonate has also been utilised intraoperatively for the treatment for severe acidemia during OLT (44,45). Reported detrimental cardiovascular effects of acidemia include impaired cardiac contractility, reduced resuscitability from induced ventricular fibrillation and altered renal blood flow (46,47,48). Acidemia may also decreases the binding of noradrenaline to its receptors, precipitate or worsen pulmonary hypertension, and increase the severity of hyperkalemia, all of which can be detrimental during liver transplantation, particularly at the time of reperfusion. However, use of sodium bicarbonate to treat acidemia in the treatment of critically ill patients remains controversial. This has been borne out in several studies that showing that severe acidemia may have protective effects, with no deleterious effects seen observed with pH as low as 6.9. Severe acidemia shifts the oxyhemoglobin curve to the right, allowing more O2 to be released (the Bohr Effect). There is also an evolving body of evidence suggesting that acidosis mediates biologically important protective effects on the myocardial (49), brain (50) and liver (51). These findings are supported by our study where we observed no differences in use of intraoperative vasoactive drugs, complications and length of ICU stay despite a significant attenuation in the degree of metabolic acidosis. At present there is no evidence that correction

of intraoperative acidosis with sodium bicarbonate leads to improved outcomes following OLT.

Our study has several methological strengths. It is a double blind randomized study, thus minimizing selection and assessment bias and increasing internal validity. The concealment of the intervention, comprehensive data collection and cross-checks enabled detailed quantitative comparisons. Our hospital shares all of the typical characteristics of major tertiary institutions in developed countries undertaking liver transplantation, providing a degree of external validity to our results. The primary end point was an objective variable not amenable to ascertainment bias or manipulation and its findings were strengthened by measurements of ancillary and more sensitive markers of changes in renal function such as eGFR, serum creatinine and cystatin. Serum cystatin has been reported to be less dependent on age, sex, race and muscle mass when compared to serum creatinine (52-56) and therefore could be an attractive renal biomarker of 'preclinical' kidney dysfunction, particularly in the setting of liver transplant associated AKI. The use of cystatin alone or in combination with creatinine has been shown to strengthen the association between the eGFR and the risks of death and end-stage renal disease across diverse populations (57,58).

There are also several limitations to our study. First, the trial was small and only powered to demonstrate major changes in renal outcome. Thus, it carried a risk of type II error. The incidence of AKI in this study (34%) was surprisingly lower than that those reported from our initial audit data (55%). Our criterion used to define AKI has not changed, and there have been no significant changed to our surgical or anesthesia technique. One explanation may be that during the audit period, the average MELD score for our patients was 24 which is higher than the average MELD score for patients in the present study. It is also possible that with better donor and graft selection, and less marginal grafts, these may have all contributed to this difference, however these differences were not explored in the initial audit, therefore direct comparisons are not possible. However, all markers of renal function failed to show even a trend in favor of sodium bicarbonate compared with saline. Second, the diagnosis of AKI relies on a surrogate measure of GFR i.e. creatinine. Differences in age, sex, dietary intake, and muscle mass, all of which can be variable in patients undergoing liver

transplantation, can result in significant variations in the serum creatinine concentration (59). However, our patient groups appeared well balanced at randomization. In addition, an estimated 10–40% of creatinine is cleared by tubular secretion into urine, which hides a considerable initial decline in creatinine clearance (60). However, there are no data to suggest that sodium bicarbonate infusion would alter the tubular secretion of creatinine. Serum creatinine levels require time to accumulate before being detected as abnormal, thus leading to a potential delay in the diagnosis of AKI, and therefore may not depict real-time changes in eGFR. However, we measured serum creatinine both at the end of surgery and at 48 hours and found no differences. Finally, eGFR is known to vary based on demographic and anthropometric factors and exhibits considerable inter-individual and intra-individual variation (61). The lack of any difference in cystatin levels between the groups further supports the lack of efficacy of sodium bicarbonate as a nephro-protective agent in the context of OLT as suggested by creatinine and eGFR assessment. Finally, as the prognostic value of biomarkers of AKI in OLT remains unclear (62), measurements of biomarkers in addition to cystatin may have enabled more accurate extrapolation and expected patterns of biomarker rise and fall. These were not performed due to resource restraints.

Conclusions

In summary, our findings provide phase II level, double-blind, controlled trial evidence that compared with normal saline, sodium bicarbonate loading and infusion beginning before OLT and continuing throughout surgery attenuates metabolic acidosis but does not affect markers of renal function. Taken within the aggregate of the literature on the use of sodium bicarbonate on renal protection and the limitations of a single centre study, our findings imply lack of clinically relevant nephroprotective effect in yet another major surgical setting with a high risk of post-operative AKI. Changes in serum creatinine, eGFR and serum cystatin from baseline were not significantly different between the two groups at the end of surgery and over the first 48-hours postoperatively. In addition there were no significant differences in other key outcomes. Sodium bicarbonate cannot be advocated for the prevention of liver transplantation-associated acute kidney injury.

Acknowledgments: Nil**References**

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Table 1. Baseline characteristics in patients undergoing orthotopic liver transplantation receiving sodium bicarbonate or saline (0.9%). Values are mean (standard deviation) or number (proportion)

	Sodium bicarbonate (n = 30)	**Sodium chloride (n = 30)**
Age; years	48.6 (10.7)	52.0 (12.3)
Sex; male; n (%)	22 (73.0)	20 (67)
Weight; kg	78 (19.2)	78 (22.0)
Body mass index, kg/m^2	26 (4.9)	27 (6.3)
Indication for transplantation, n (%)		
Hepatitis B	3 (10)	2 (7)
Hepatitis C	9 (30)	11 (37)
Alcoholic cirrhosis	4 (13)	5 (17)
Acute liver failure	0	0
Liver malignancy	2 (7)	0
Other cirrhosis	12 (40)	12 (40)
Scoring Systems		
MELD	18 (6.6)	16 (4.5)
APACHE II	15 (5.3)	17 (4.6)
SAPS II	26 (7.4)	29 (9.1)
Co-morbidities, n (%)		
Hypertension	3 (10)	5 (17)
Diabetes	7 (23)	8 (27)
Ischemic heart disease	1 (3)	1 (3)
Atrial fibrillation	2 (7)	1 (3)
COPD	4 (13)	5 (17)
Laboratory results		
Standard base excess; $mmol.L^{-1}$	-1.60 (4.17)	-1.94 (4.42)
Lactate; $mmol.L^{-1}$	1.31 (0.48)	1.29 (0.55)
pH	7.38 (0.08)	7.37 (0.07)
Bicarbonate; $mmol.L^{-1}$	22.7 (3.4)	22.7 (3.9)

Sodium; mmol.L^{-1}	134 (5.3)	137 (5.4)
Chloride; mmol.L^{-1}	101 (5.8)	104 (5.8)
Potassium; mmol.L^{-1}	4.1 (0.74)	3.9 (0.49)
Magnesium; mmol.L^{-1}	0.85 (0.14)	0.82 (0.10)
Phosphate; mmol.L^{-1}	1.17 (0.24)	1.13 (0.24)
Ionised Calcium; mmol.L^{-1}	1.15 (0.06)	1.16 (0.08)
Strong ion difference; mEq.L^{-1}	34.4 (2.90)	34.9 (3.45)
Strong ion gap; mEq.L^{-1}	1.2 (3.00)	1.6 (2.66)
Albumin; g.L^{-1}	29 (7.7)	31 (8.3)
Creatinine; umol.L^{-1}	85 (40.5)	89 (37.1)
eGFR; ml.min^{-1}	77 (19.2)	70 (19)
Cystatin C; mg.L^{-1}	1.35 (0.51)	1.36 (0.55)
Hemoglobin; g.dL^{-1}	107 (23)	108 (23)

MELD: Model For End-Stage Liver Disease; APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; COPD: Chronic Obstructive Pulmonary Disease; eGFR: estimated glomerular filtration rate

Table 2. Intraoperative fluid, blood product use and requirements for vasoactive drugs in patients undergoing orthotopic liver transplantation receiving sodium bicarbonate or saline (0.9%). Values are mean (standard deviation) or number (proportion)

	Sodium bicarbonate (n = 30)	**Sodium chloride (n = 30)**	**p**
Duration of surgery, hours	9.93 (1.80)	9.92 (1.57)	0.98
Blood product requirements			
Intraoperative cell salvage, mL	1615 (1552)	2004 (1830)	0.49
Blood from donor, mL	351 (416)	377 (512)	0.88
Packed red blood cells, units	3.13 (4.25)	3.50 (3.37)	0.44
Fresh frozen plasma, units	1.88 (2.13)	2.08 (2.08)	0.74
Cryoprecipitate, units,	2.74 (5.15)	2.55 (3.97)	0.90
Pooled platelets, units	1.04 (1.46)	0.71 (1.16)	0.49
Colloid and crystalloid infusion, mL			
Human albumin 20%	839 (598)	879 (588)	0.55
Plasma-Lyte148®	5240 (4726)	5114 (4996)	0.79
Compound sodium lactate	237 (514)	143 (359)	0.43
Urine output, mL	1054 (713)	954 (763)	0.42
Vasoactive drugs			
Patients requiring norepinephrine, n (%)	29 (97)	29 (97)	1.0
Median amount of norepinephrine, ug	1300	1200	0.77

Patients requiring metaraminol, n (%)	30 (100)	30 (100)	1.0
Median amount of metaraminol, mg	6.0	6.2	1.0

Table 3. Clinical chemistry in patients undergoing orthotopic liver transplantation receiving sodium bicarbonate or saline (0.9%). Values are mean (standard deviation)

	Immediately postoperatively			48 hours postoperatively		
	Sodium bicarbonate (n = 30)	**Sodium chloride (n = 30)**	**p**	**Sodium bicarbonate (n = 30)**	**Sodium chloride (n = 30)**	**p**
Standard base excess; mmol.L^{-1}	-0.53 (2.87)	-3.70 (3.59)	<0.001	0.53 (3.17)	-1.07 (3.89)	0.09
Lactate; mmol.L^{-1}	2.12 (1.62)	3.14 (2.44)	0.20	1.41 (0.75)	1.64 (1.89)	0.89
pH	7.38 (0.06)	7.34 (0.05)	0.001	7.40 (0.04)	7.39 (0.06)	0.40
Bicarbonate; mmol.L^{-1}	24.0 (2.7)	21.5 (3.2)	0.002	24.8 (3.3)	23.3 (3.8)	0.12
Sodium; mmol.L^{-1}	138 (4.9)	140 (3.5)	0.09	138 (6.2)	140 (4.8)	0.34
Chloride; mmol.L^{-1}	103 (4.3)	106 (4.9)	0.01	104 (5.5)	107 (4.3)	0.03
Potassium; mmol.L^{-1}	4.1 (0.78)	4.1 (0.59)	0.68	4.4 (0.51)	4.1 (0.47)	0.02
Magnesium; mmolL^{-1}	0.93 (0.18)	0.88 (0.26)	0.44	1.05 (0.18)	0.97 (0.19)	0.12
Phosphate; mmol.L^{-1}	1.58 (0.52)	1.57 (0.43)	0.96	1.66 (0.57)	1.55 (0.45)	0.43
Ionised Calcium; mmol.L^{-1}	1.16 (0.07)	1.18 (0.09)	0.37	1.14 (0.06)	1.16 (0.08)	0.36
Strong ion difference; mEq.L^{-1}	39.5 (3.11)	36.9 (3.54)	0.49	39.1 (3.41)	37.9 (3.75)	0.46
Strong ion gap; mEq.L^{-1}	3.72 (1.79)	4.35 (2.88)	0.01	2.93 (2.91)	3.19 (2.64)	0.61
Albumin; g.L^{-1}	32 (5.7)	32 (5.9)	0.82	30 (4.7)	31 (5.2)	0.38
Hemoglobin; g.dL^{-1}	93.8 (15.8)	102 (17.8)	0.05	87.1 (14.2)	88.6 (13.2)	0.51

Table 4. Primary and secondary outcome measures in patients undergoing orthotopic liver transplantation receiving sodium bicarbonate or saline (0.9%).

	Sodium bicarbonate (n = 30)	**Sodium chloride (n = 30)**	**p**
Renal function outcome measures at 48 hours postoperatively:			
Acute kidney Injury: n (%)	11 (37)	10 (33)	1.0
Acute kidney injury: RIFLE Class 'R', n (%)	6 (20)	4 (13)	0.7
Acute kidney injury: RIFLE Class 'I', n (%)	3 (10)	3 (10)	1.0
Acute kidney injury: RIFLE Class 'F', n (%)	2 (7)	3 (10)	1.0
Creatinine, umol.L^{-1}	116 (69.5)	123 (87.2)	0.86
eGFR, ml.min^{-1}	65 (26.2)	60 (25.7)	0.40
Cystatin C, mg.L^{-1}	1.72 (0.74)	1.73 (0.73)	0.95
Postoperative acidosis: pH < 7.35, n (%)	10 (33)	15 (50)	0.29
Postoperative alkalosis: pH > 7.45, n (%)	3 (10)	3 (10)	1.0
Patients with at least one post-operative complication, n (%)	28 (93)	28 (93)	1.0
Clavien-Dindo grade of highest complication; n (%)	7 (23)	5 (17)	0.75
Grade I	16 (53)	18 (60)	1.0
Grade II	1 (3)	1 (3)	1.0
Grade III	4 (14)	4 (14)	1.0
Grade IV	0	0	
Grade V	0	0	
Cardio-respiratory complications, n (%)			
Pneumonia	5 (17)	11 (37)	0.14
Acute respiratory distress syndrome	3 (10)	3 (10)	1.0
Pleural effusion	2 (7)	3 (10)	1.0
Cardiac arrhythmia	4 (13)	10 (33)	0.13

Myocardial infarction	0	0	1.0
Cardiac arrest	0	3 (10)	0.24
Surgical complications, n (%)			
Graft rejection	1 (3)	4 (13)	0.35
Bleeding requiring surgical intervention	2 (7)	1 (3)	1.0
Bile leak	0	0	1.0
Sepsis	5 (17)	7 (23)	0.75
Vascular thrombosis	1 (3)	1 (3)	1.0
Other complications, n (%)			
Delirium	7 (23)	12 (40)	0.27
Hospital outcomes, median (IQR)			
ICU stay (hours)	35 (30:42)	38 (30:50)	0.46
Time on ventilator support (hours)	10 (8:13)	14 (9:18)	0.02
Time on inotropic support (hours)	4 (1:8)	9 (5:13)	0.03
Length of hospital stay (days)	13.0 (10:17)	15 (11:21)	0.18