Perioperative Evolution of Sodium Levels in Cirrhotic Patients Undergoing Liver Transplantation: An Observational, Prospective Study

ido zamberg (✉ idozamberg@gmail.com)

University Hospital of Geneva <https://orcid.org/0000-0003-4534-4635>

Julien Maillard

Hopitaux Universitaires de Geneve

Simon Tomala

Hopitaux Universitaires de Geneve

Benjamin Assouline

Hopitaux Universitaires de Geneve

Gleicy Keli-Barcelos

Hopitaux Universitaires de Geneve

Florence Aldenkortt

Hopitaux Universitaires de Geneve

Thomas Mavrakanas

Hopitaux Universitaires de Geneve

Axel Andres

Hopitaux Universitaires de Geneve

Eduardo Schiffer

Hopitaux Universitaires de Geneve

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Abstract

Background & Aims: Hyponatremia is an important predictor of early death among cirrhotic patients in the orthotopic liver transplantation (OLT) waiting list. Evidence exists that prioritizing OLT waiting list according to the MELD score combined with plasma sodium concentration might prevent pretransplantation death. However, the evolution of plasma sodium concentrations during the perioperative period of OLT is not well known. We aimed to describe the evolution of perioperative sodium concentration during OLT and its relation to perioperative neurohormonal responses.

Methods: Twenty-seven consecutive cirrhotic patients who underwent OLT were prospectively included in the study over a period of 27 months. We studied the evolution of plasma sodium levels, the hemodynamics, the neurohormonal response and other biological markers during the perioperative period of OLT.

Results: All patients with a hyponatremia before OLT were in the Child C group. None of the patients had acute or chronic renal impairment. Interestingly, in patients with hyponatremia, plasmatic sodium reached normal levels as soon as the injured livers were removed during surgery and the plasma sodium concentration remained within normal ranges 1 day, 7 days, as well as 6 months after surgery.

Conclusions: *Further investigation of rapid correction and stabilization of sodium levels after OLT, as observed in our study, would be of interest in order to fully understand the mechanisms involved in cirrhosis related hyponatremia, its prognostic value and clinical implications.*

Introduction

Patients with compensated cirrhosis have an imbalance of sodium excretion. While the glomerular filtration rate remains within normal values, an increased sodium tubular reabsorption decreases urinary sodium excretion. Following a sodium load, kidneys are incapable to excrete additional sodium overload. Activation of the mineralocorticoid receptor by aldosterone [1, 2] or cortisol (in patients with impaired 11 β -hydroxysteroid dehydrogenase activity) [3] would explain mentioned sodium reabsorption. In contrast to patients without end-stage liver disease who can excrete a solute-free water overload, most cirrhotic patients with ascites cannot. The impaired solute-free water excretion is the consequence of increased secretion of arginine vasopressin from the neurohypophysis stimulated by arterial underfilling [1, 4]. In normal subjects, osmotic stimulus controls arginine vasopressin secretion while in patient with advanced cirrhosis, arterial underfilling by decreasing the stretch on arterial baroreceptors, overrides the osmotic stimulus and stimulates the synthesis and release of the hormone. In this group of patients who retain solute-free water in an amount disproportionate to sodium retention, hyponatremia occurs concomitantly to an increase in extracellular fluid volume. Additionally, patients with cirrhosis and ascites may develop a rapidly progressive (type 1) or more insidious (type 2) functional renal failure also known as hepatorenal syndrome [5, 6].

Low plasma sodium concentration is an important predictor of early death in cirrhotic patients on the waiting list for orthotopic liver transplantation (OLT) [7–12] and is also associated with an increased number of complications following OLT regardless of the clinical condition causing hyponatremia [13–15]. Whether the prognostic value of hyponatremia is due to the fact that it is a marker of the disease's stage, its direct negative effects on several organs's function or both is unknown [8]. Kim et al. [16] had shown, through a retrospective analysis of adult candidates registered within the Organ Procurement and Transplantation Network in 2005 and 2006, that prioritizing OLT waiting list according to the MELD score combined with plasma sodium concentration could have prevented deaths within patients in the list.

In addition, Sharma [17] and al. have also shown an increase in survival rate related to hyponatremia among patients with MELD scores > 11 providing more evidence to the importance of sodium control in the pre-OLT period.

While it seems clear that hyponatremia is a risk factor for mortality in the pre-OLT period, the evolution of sodium levels and its relation to neurohormonal response during the perioperative period of OLT is unknown. In this observational, prospective study, we monitored plasma sodium concentration and multiple biological markers including the neurohormonal response in the perioperative period of OLT in 27 consecutive patients who underwent OLT in our institution.

Patients And Methods

Patient selection

Twenty-seven consecutive patients (age 56 [23–65] years) were prospectively included in the study over a period of 27 months. Sample size correlates to the annual average number of liver transplantations in our institution. The ethics committee of our institution (Hôpitaux Universitaires de Genève, Geneva, Switzerland) approved the protocol and written informed consent was obtained from each patient at the time of inclusion in the waiting list.

The study protocol was registered in the ISRCTN register (N° 43452247) with the objective to describe the renal and neurohormonal responses during liver transplantation. In current study we analysed data concerning variations in serum sodium levels. In fact, there is increasing evidence showing the importance of hyponatremia as an independent predictor of mortality after listing for OLT [7, 8, 12, 14, 15], and as so, its potential value in prioritizing patients for OLT.

Preoperative evaluation (PRE_{OLT})

Patients were included at the time they were admitted in the waiting list for OLT. Assessment of liver disease was based on medical history, physical examination, laboratory tests, hemodynamic parameters, liver imaging and histology. The evolution of the disease during the waiting period was assessed every three months. PRE_{OLT} parameters were recorded during the last patient evaluation preceding OLT. Two groups of patients were compared according to the severity of liver disease assessed by the Child-Pugh

score: patients with mild or moderate liver dysfunction (child A or B scores, Child_{AB} group) and patients with severe liver dysfunction (Child C score, Child_C group).

Anesthetic management and surgery

Anesthesia was induced with continuous infusion of midazolam, sufentanyl, and atracurium with conformity to our institution's protocol. Each patient has a radial artery catheter for continuous arterial blood pressure monitoring and blood sampling, a triple-lumen central venous catheter (HydrocathA, Ohmeda, Swindon, UK) for fluid perfusion and drug administration, and a flow-directed thermodilution pulmonary artery catheter (CCOmbo, Edwards Lifesciences, Irvine, CA, USA) for pulmonary artery pressure, mixed venous oxygen saturation (SvO₂), and cardiac output measuring (Vigilance, Edwards Lifesciences, Irvine, CA, USA). Perioperative normothermia [35.5–37 °C] was maintained with warming blankets. Following resection of the native liver, graft implantation was performed with end-to-end anastomosis. To avoid congestion of splanchnic organs, renal hypertension, and decreased venous return induced by the concomitant cross-clamping of portal vein and inferior vena cava, a bypass was placed according to the hemodynamic tolerance to portal and inferior vena cava clamping. Indications for porto-femoral to axillary vein bypass were a decreased (> 30%) cardiac index or decrease in mixed-venous hemoglobin oxygen saturation below 70% when clamping both the portal vein and the inferior vena cava. The extracorporeal system included a nonocclusive centrifugal pump (model 540 Bio-Medicus, Medtronic, Kerkrade-West, Holland), heparin-coated tubings (Medtronic, Kerkrade-West, Holland) and catheters (Carmeda AB, Töby, Sweden).

Liver grafts that had been preserved at 4 °C in University of Wisconsin solution were flushed after the completion of the lower caval anastomosis with 4% human albumin (ZLB Behring AG, Bern, Switzerland) to obtain potassium concentrations in the outflow perfusate that steadily decreased below 12 mmol/l. After upper caval and portal anastomosis, the graft was revascularized with portal flow and the venovenous bypass terminated. Hepatic artery anastomosis followed by bile duct reconstruction was then performed.

To maintain stable hemodynamic parameters, crystalloids (Ringer lactate containing 6 g/L sodium salts) were infused at a rate of 5 to 10 mL/kg/hour to maintain the following criteria: heart rate < 100 beats per min, mean arterial pressure > 60 mmHg, right atrial pressure between 5 and 10 mmHg and pulmonary artery occlusion pressure between 8 and 14 mmHg. Red blood cells (in saline adenine glucose–mannitol solution) were transfused when serum hemoglobin concentration was ≤ 8 g/dl during surgery and ≤ 9 g/dl in the postoperative period. Fresh-frozen plasma was administered according to coagulation status as documented by thromboelastography and according to surgical clinical assessment of bleeding during surgery. Platelets were transfused during per and post - operative periods when platelets count decreased below 30,000 per mL. No other coagulation factors were administered, and no intraoperative blood salvage was used. All intravenous fluids except platelets were administered through a fluid warming device.

Hemodynamic measurements and blood collection in the perioperative period

Blood samples (20 mL) and urine samples (5 mL) were collected 1 hour after induction of anesthesia (ANE sample), at the end of the anhepatic phase (ANH sample), one hour after graft reperfusion (POST_{1h} sample), and in the ICU at 24 hours (POST_{24h} sample) after liver reperfusion. At each time point, systemic and pulmonary hemodynamic parameters and urine flow were measured. The creatinine clearance was calculated according to the Cockcroft-Gault formula. Plasma Cystatin C was also measured in the perioperative period. Sodium excretion fraction was calculated according to following formula: $FE_{NA} = ([\text{urine sodium}] \times [\text{plasma creatinine}]) / ([\text{plasma sodium}] \times [\text{urine creatinine}])$. Sodium concentration was measured within plasma, serum and urine using indirect potentiometry.[18]

Hormone measurements

Blood samples were collected into tubes containing ethylene diamine tetra acetic acid. Tubes were placed on ice and thereafter centrifuged for 15 min at 2000 g (2–8 °C). Plasma samples were stored at -80 °C until analysis.

Plasma renin activity was assessed at 37 °C by direct radioimmunoassay measurement of angiotensin I production from endogenous substrates. In our institution, renin activity in supine position ranges from 0.23 to 1.55 ng/mL/hour. Free catecholamines were measured by liquid chromatography with amperometric detection. Blood (1 mL) was extracted on activated alumina at pH 8.6 and catecholamines were eluted in acidic media before injection into the chromatographic system. The detection limit was 10 pg/injection. Arginine vasopressin was determined by a radioimmunoassay after an extraction procedure using a reversed-phase column extraction according to the manufacturer's instructions (Bühlmann Laboratories AG, Allschwil, Switzerland). Relative affinity of the vasopressin antiserum was given as follows: 100% for arginine vasopressin, 0.25% for lysine vasopressin, and 0.001% for oxytocin and vasotocin. The detection limits were 0.35 pg/mL or 0.32 pmol/L of plasma. Plasmatic NT-proBrain Natriuretic Peptide (pro-BNP) was assessed on Elecsys (Roche, Basel, Switzerland) and DXI (Beckman Coulter, Brea, CA, USA) auto-analysers. NTpro-BNP < 125 pg/mL are considered as normal values.

Postoperative evaluation (POST_{OLT})

Biological parameters were evaluated in all patients 1 hour, 24 hours and 6 months after OLT (POST_{OLT}).

Data analysis

Data are median [minimum - maximum]. In the perioperative periods (ANE, ANH, POST_{1h}, POST_{24h}), variables were compared by MANOVA with repeated measurements (time) versus treatment (Child group) using SAS JMP[®] version 14.0. Macuhy's test of sphericity was then conducted to test for violation of sphericity. If the sphericity chi-square was significant p values were shown according to Greenhouse-Geiser (G-G) multivariate test. However, if sphericity chi-square was not significant p values shown were

the univariate unadjusted values. Other variables were compared by a Mann-Whitney test or Kruskal-Wallis analysis with posthoc Dunn test using IBM♥ SPSS♥ Version 15.

Results

Characteristics of patients and surgery

Between August 2010 and November 2015, twenty-seven patients consisting of 22 males and 5 females who underwent OLT were prospectively included at our institution. Characteristics of patients are summerized in Table 1. The etiologies of cirrhosis were: alcohol abuse (n = 9), hepatitis (n = 13), biliary (n = 2), and others (n = 3).

Table 1
Characteristics of patients and surgical intervention

	Child _{AB} patients (n = 14)	Child _C patients (n = 13)	p
Age [yr]	57 [29–65]	52 [23–65]	0.37
Gender	13	9	
Male [n]	1	4	
Female [n]			
BMI [kg/m ²]	25 [15–32]	28 [20–40]	0.20
MELD	10 [6–13]	15 [12–37]	< 0.001
HVPG [mmHg]	11.36 [6–16]	19 [13–24]	0.012
Time on waiting list [days]	296 [59-1307]	261 [5-675]	0.34
Graft donors [n]	1	0	
Living	13	13	
Cadaver			
Split livers [n]	1	1	
Retransplantations [n]	0	1	
Veno-venous bypass [n]	5	5	
Anhepatic phase [min]	71 [48–124]	70 [62–103]	0.56
Cold ischemia [min]	481 [163–719]	503 [331–752]	0.25
Transfusion requirements during surgery [U]	2.5 [0–12]	4 [0–9]	0.18
Red blood cells	2.5 [0–11]	9 [3–20]	0.005
Fresh frozen plasma	0 [0–1]	0 [0–2]	0.41
Platelets			
Stay in ICU (days)	5 [2–21]	4 [3–9]	0.66
Late death [n]	1	1	

Two groups of patients were compared: Child_{AB} and Child_C groups. One patient obtained a living donor, and two had split livers. The remaining patients received whole cadaveric liver graft, including one for retransplantation. Among all patients, ten had venovenous bypass (five in each group). Before surgery, the time spent on the waiting list was similar in Child_{AB} and Child_C groups. During surgery, the anhepatic

phase and cold ischemia did not differ between the two groups. Red blood cells and platelet requirements were similar in Child_{AB} and Child_C groups, but the Child_C group received more fresh frozen plasma units. One patient died during the study period in each group. The time spent in ICU was similar in the two groups.

Plasma sodium concentration and OLT

Hyponatremia was defined by a sodium levels < 135 mmol/l as per standard definition [19].

All patients with Pre_{OLT} hyponatremia were in the Child_C group and the preoperative plasma sodium concentration was significantly lower in Child_C than in Child_{AB} groups (Table 2 and Fig. 1A, $p < 0.02$). In Child_C patients, four out of thirteen (30%) had a plasma sodium concentration of less than 135 mEq/l. Interestingly, plasma sodium concentrations varied during the observation period and hyponatremia occurred concomitantly to complications (digestive hemorrhage, bacterial peritonitis and decompensated ascites) as illustrated in Fig. 2. During the perioperative surgical period, the sodium concentration did not change significantly in Child_{AB} patients while within Child_C sodium levels reached normal levels during the anhepatic phase (ANH) ($p = 0.02$, Fig. 1B).

Table 2
Renal function in the preoperative period (PRE_{OLT}) and 6 months after OLT (POST_{OLT})

	PRE _{OLT}	POST _{OLT}	p
Plasma Na [mmol/l]	137 [135–142]	138 [133–143]	1.000
Child _{AB}	133 [125–141]	140 [134–142]	0.002
Child _C			
Plasma creatinine [μmol/l]	80 [56–100]	97 [63–140]	0.009
Child _{AB}	89 [58–152]	90 [62–135]	0.497
Child _C			
Creatinine clearance	86 [44–157]	60 [45–124]	0.11
Child _{AB}	85 [38–162]	74 [38–117]	0.64
Child _C			
Cystatine-C	1.12[0.74–2.14]	1.11 [0.74–1.65]	0.394
Child _{AB}	1.21[0.74–2.01]	1.30 [1.22–3.16]	0.02
Child _C			
FENa [%]	0.7 [0.0-3.1]	0.5 [0.3–3.1]	0.98
Child _{AB}	0.2 [0.0-3.7]	0.9 [0.1–2.1]	0.07
Child _C			
Loop diuretics/spironolactone	5/5	1/0	
Child _{AB}	8/7	1/0	
Child _C			
Data are median [minimum - maximum]. p from Mann Whitney analysis between			
PRE _{OLT} and POST _{OLT} .			

To be noted, correction of hyponatremia in the Child_C group was not associated with adverse outcomes. Specifically, no central pontine myelinolysis was observed. Plasma sodium concentrations remained in normal range and similar in both groups seven days ($p = 0.63$, Fig. 1C) and six months (POST_{OLT}, $p = 0.56$, Fig. 1D) after OLT. Four patients in the Child_C group remained with a plasma sodium concentration lower than 135 mEq/L at day seven after OLT. The latter was not associated with worst outcomes in the

observation period. Sodium levels normalized after in three out of these four patients. FE_{NA} of Child_C patients did not significantly increase from the PRE_{OLT} to the POST_{OLT} periods (Table 2, $P = 0.07$).

Systemic hemodynamic and biological parameters in the perioperative period

Pulmonary and systemic hemodynamics were measured after induction of anesthesia (ANE), during the ANH, 1 hour (POST_{1h}) and 24 hours (POST_{24h}) after graft reperfusion. There was no difference between the two patient groups for mean arterial pressure ($p = 0.89$), heart rate ($p = 0.81$), and cardiac index ($p = 0.14$) (Fig. 3). In contrast, Child_{AB} patients had higher systemic vascular resistance values than Child_C during the ANE period but, in the POST_{1h} and POST_{24h} periods, both groups had similar values (Fig. 3). Pulmonary vascular resistance index was significantly lower in the Child_C group ($p = 0.02$) while mean pulmonary arterial pressures did not differ between groups during the observed period (Table 3). The alveolo-arterial gradient of PO_2 (AaDO₂, mmHg) transiently increased in the Child_C group during the ANE and POST_{1h} periods but both groups had similar AaPO₂ 24 h after graft reperfusion. Plasma lactate concentrations similarly increased in both groups in the ANE and POST_{1h} periods while arterial pH steadily decreased over time in both groups without any significant difference between groups. Hematocrit, which was lower in Child_C group during the ANE period comparing to the Child_{AB}, similarly decreased in both groups during the observed period (Table 3).

Table 3

Systemic and pulmonary hemodynamics and additional measurements during the perioperative period of OLT

	PRE	ANH	POST _{1h}	POST _{24h}	p1 (p value over time)	p2 (p value between groups)
SVRI						
Child _{AB}	1696.47 [926.3–3163.6]	2694.02 [1406.1–4285.7]	1137.95 [685.7–2526.3]	1546.65 [1126.5–3138.5]	< 0.0001	0.57
Child _C	1142.90 [740.7–3345.5]	1714.29 [1180–4571.4]	1131.70 [800–1685.7]	1624.2 [714.3–2258.8]		
PVRI						
Child _{AB}	159 [30–542]	252 [77–495]	133 [14–450]	117 [16–523]	0.01	0.02
Child _C	102 [19–193]	133 [57–286]	156 [77–343]	130 [22–447]		
CI						
Child _{AB}	3.1 [1.9–5.7]	2.05 [1.4–3.3]	4.3 [1.9–5.9]	4.1 [2.6–5.0]	< 0.0001	0.14
Child _C	4.4 [2.2–5.9]	2.7 [1.4–4.0]	4.5 [2.8–5.4]	4.3 [3.3–5.6]		
CVP						
Child _{AB}	8.5 [1–13]	7 [1–12]	10.5 [1–14]	8 [5–14]	0.18	0.43
Child _C	10 [0–22]	7 [0–14]	8 [0–16]	9 [5–14]		
AaDO ₂						
Child _{AB}	18 [13–32]	25.5 [7–62]	18 [8.5–69]	8 [4–15]	< 0.0001	0.39
Child _C	21 [7–31]	28 [14–60]	25 [12–75]	6.5 [3.5–13]		
MPAP						

Data are median [minimum – maximum]; Systemic Vascular Resistance Index (SVRI, (dynes .. sec .. cm⁻⁵)/m²); Pulmonary Vascular Resistance (PVRI, (dynes .. sec .. cm⁻⁵)/m²). Alveolo-arterial gradient of PO₂ [AaPO₂, mmHg]; Lactates [mmol/L]; Hematocrit [%], Central Venous Pressure (PVC, mmHg), Mean Pulmonary Arterial Pressure (MPAP, mmHg), Cardiac Index (CI, L/min/m²). p from MANOVA with repeated measures. p1 represents changes in parameters over time within both groups whereas p2 represents interaction between time and Child.

	PRE	ANH	POST _{1h}	POST _{24h}	p1 (p value over time)	p2 (p value between groups)
Child _{AB}	16 [11–32]	13 [10–24]	18 [9–28]	18 [13–29]	< 0.0001	0.16
Child _C	18 [5–29]	12 [6–21]	17 [12–27]	18 [10–31]		
Lactates						
Child _{AB}	1.0 [0.4–2.2]	2.4 [1.1–4.2]	1.7 [0.8–7.3]	1.1 [0.5–2.2]	< 0.0001	0.21
Child _C	1.5 [0.5–3.2]	2.9 [1.7–7.0]	2.6 [1.1–7.0]	0.8 [0.4–1.5]		
Arterial pH						
Child _{AB}	7.42 [7.29–7.53]	7.36 [7.30–7.51]	7.35 [7.25–7.42]	7.37 [7.24–7.4]	0.001	0.98
Child _C	7.45 [7.35–7.56]	7.41 [7.28–7.49]	7.41 [7.10–7.50]	7.39 [7.35–7.43]		
Hematocrit						
Child _{AB}	36 [28–45]	31 [20–45]	28 [23–44]	30 [23–45]	0.001	0.35
Child _C	30 [22–42]	26 [22–41]	26 [21–33]	26 [23–33]		
Data are median [minimum – maximum]; Systemic Vascular Resistance Index (SVRI, (dynes .. sec .. cm ⁻⁵)/m ²); Pulmonary Vascular Resistance (PVRI, (dynes .. sec .. cm ⁻⁵)/m ²). Alveolo-arterial gradient of PO ₂ [AaPO ₂ , mmHg]; Lactates [mmol/L]; Hematocrit [%], Central Venous Pressure (PVC, mmHg), Mean Pulmonary Arterial Pressure (MPAP, mmHg), Cardiac Index (CI, L/min/m ²). p from MANOVA with repeted mesures. p1 represents changes in parametres over time within both groups whereas p2 represents interaction between time and Child.						

Renal and Neurohormonal responses during surgery and 24 h after graft reperfusion

During the perioperative period, plasma concentrations of creatinine ($p = 0.11$, Table 2) and the creatinine clearance ($p = 0.64$) did not differ between both groups, while cystatin C concentrations significantly but moderately increased in the Child_C group at POST_{24h}. ($P < 0.005$, Table 2). Urine flow was higher during the POST_{1h} period in Child_{AB} patients ($p = 0.01$).

The plasma renin activity and concentrations of epinephrine, vasopressin, and brain natriuretic peptide increased during the anhepatic period and returned to normal values in the consecutive periods for most patients (Table 4).

Table 4
Neurohormonal responses during surgery and 24 h after graft reperfusion

	PRE	ANH	POST _{1h}	POST _{24h}	p1 - value over time	p2 - value over time and between groups
FE _{Na} [%]	1.0 [0.1– 2.1]	0.7 [0.1–2.3]	1.2 [0.1– 3.3]	0.3 [0.1– 3.4]	0.18	0.81
Child _{AB}		0.5 [0.1–2.6]		0.5 [0.1– 2.2]		
Child _C	0.6 [0.1– 1.7]		0.8 [0.1– 2.7]			
Renin activity	2 [1– 13]	10 [1–40]	2 [1– 26]	2 [1–14]	0.0004	0.12
Child _{AB}	5 [1– 45]	17 [1–87]	3 [1– 35]	3 [1–3]		
Child _C						
Epinephrine	1 [1– 3]	3 [1–6]	1 [1–4]	1 [1–2]	0.006	0.69
Child _{AB}		3 [1–11]	1 [1–6]	1 [1–1]		
Child _C	1 [1– 4]					
Vasopressin	2 [1– 45]	5 [1–14]	2 [1– 12]	4 [1–15] 2 [1–5]	0.26	0.48
Child _{AB}		5 [3–19]				
Child _C	5 [2– 14]		3 [1– 14]			
Pro-BNP	429 [20– 1830]	15691 [2175– 27553] 5552 [2277–35164]	1556 [154– 6796]	636 [41– 11602]	< 0.01	0.32
Child _{AB}				865 [247– 10949]		
Child _C	154 [20– 1839]		3445 [133– 48780]			
Data are median [minimum - maximum]; Renin activity [normal value: 0.23–1.55 ng/mL/hour]; Epinephrine [nmol/l]; Vasopressin [pg/ml]; Pro-brain natriuretic peptide [Pro-BNP, normal value: < 125 pg/mL]; p with a MANOVA with repeated measures analysis. p from MANOVA with repeated measures. p1 represents changes in parameters over time within both groups whereas p2 represents interaction between time and Child.						

Discussion

Description of the perioperative evolution of sodium levels and neurohormonal response in patients with cirrhotic liver disease undergoing OLT was the main objective of our study. All patients with hyponatremia were in the Child_C group. Interestingly, low plasma sodium concentration was corrected rapidly after

cirrhotic liver was removed and the plasma sodium concentration remained within normal ranges 1 day, as well as 6 months after surgery. This correction was not associated with adverse outcomes within study's observation period. Specifically, no central pontine myelinolysis was observed.

Hyponatremia in cirrhosis is primarily the result of solute-free water retention exceeding that of sodium [20]. The proposed mechanism is splanchnic arterial vasodilatation leading to reduced systemic vascular resistance and the release of various neurohormones. An arterial underfilling is sensed by baroreceptors and activates a compensatory neurohumoral response through the sympathetic nervous system, the renin-angiotensin-aldosterone system, as well as the release of arginine vasopressin. The net result of this activation is solute-free water retention, intense renal sodium retention, and hypervolemic hyponatremia. The degree of activation of these neurohumoral mechanisms correlates directly to the degree of portal hypertension [21]. Serum sodium concentration is therefore an important parameter to be considered before OLT as it might reflect the severity of the disease.

Several studies emphasize the importance of sodium levels in the assessment for OLT priority within potential candidates. Hyponatremia < 130 mmol/L was shown to be an independent predictor of mortality after listing, as lower sodium levels at inclusion in the waiting list were associated with 3- and 12-month decreased survival [7]. A clear cutoff for the association between hyponatremia and survival after listing is not yet well defined and differs between studies: < 135 mmol/L [22], < 130 mmol/L [23], or 126 mmol/L [24] respectively. The mortality risk might also be inversely correlated to the plasma sodium concentrations [16, 25]. Consequently, several MELD-derived scores that incorporate plasma sodium concentration proposed to include hyponatremia as a priority criterion for OLT. The prevalence of hyponatremia in OLT candidates varies from 11–34%. It is 21.6% (cutoff at 130 mmol/L) or 49.4% (cutoff at 135 mmol/L) in the overall population of cirrhotic patients. In our study, hyponatremia was present in four patients (30%, cutoff at 135 mmol/L). None of the patients had a sodium concentration lower than 120 mEq/L.

The predictive effect of sodium concentration was shown to be greater within patients with low MELD SCORE. Thus, in the same way that serial MELD scores predict mortality better than a single value, serial measurements of plasma sodium could have a better predictive value than a single measurement [16]. While awaiting OLT, hyponatremia is likely to fluctuate over time concomitantly with the complications of cirrhosis and the patient treatment [26, 27]. This fluctuation was reproduced in our study (see Fig. 2). The number of acute aggravations and the ability to recover would probably be a factor of interest at the time of OLT listing and should be further studied. An increased risk of death is associated with a serum sodium concentration < 126 mmol/L (6.5fold increase) or < 131 mmol/L (5-fold increase) measured at any time during the waiting period for OLT [25]. In our study, a serum sodium concentration < 131 mmol/L at the time of listing was not associated with an increased risk of death at 6 months following OLT. The fact that sodium levels fluctuate before OLT and that hyponatremia seem to have predictive effect for postOLT increased mortality might strengthen the importance of studying the effect of serial sodium concentration measuring before OLT as they could provide a fuller picture of postOLT mortality risk.

In addition, Hyponatremia prior to OLT was associated with an increased 90-day postoperative mortality [14]. Similarly, in patients with cirrhosis, hyponatremia at time of OLT (< 130 mmol/L) was shown to increase the risk of postoperative neurologic disorders, infectious complications, and renal failure during the first month after OLT and reduced the 3-month survival rate [13]. However, the postOLT outcome highly depends on donor characteristics, cardiovascular evolution during liver replacement, and surgical complications. In our study, sodium levels were significantly lower in patients with severe liver failure before OLT. Sodium correction took place during OLT before the surgical anhepatic phase (Fig. 1), reaching similar normal values in both groups. None of the patients experienced neurological complications due to this rapid correction of sodium concentration.

Correction of hyponatremia following OLT and its outcomes seems to be a matter of debate. Few studies have focused on the fluctuations of sodium levels during and after OLT. Both, Romanovski et al. [28] and Hudcova et al. [29], have shown that rapid correction of natremia after OLT in hyponatremic patients was associated with worse outcomes and complications in the post operative period of OLT. Similarly, Park et al. [30] has found that major shift of natremia during OLT with liver donor was a risk factor for prolonged mechanical ventilation post transplantation. In contrast, the study from Brandmann et al. [31] paying particular attention to the consequences of fluctuations in sodium levels in patient with hepatic encephalopathy before OLT, showed that there was no influence on neurological outcome or length of stay in ICU. Leise and al [32] have even found that hyponatremia was not associated with worse outcomes unlike hypernatremia before OLT. In our study, natremia correction was not associated with negative outcomes and the time spent in ICU after OLT was not significantly longer in patients with hyponatremia.

Another interesting observation of our study is that hyponatremia coexists with most complications of cirrhosis as previously reviewed by Schrier et al. [1, 4] (Fig. 4). Activation of arterial baroreceptors occurs with low cardiac output (cirrhotic cardiomyopathy or decreased preload) as well as high cardiac output (septic-like syndrome/inflammation) and exacerbation of splanchnic vasodilatation with increased portal pressure [1, 4, 33]. This unifying hypothesis further reinforces the usefulness of hyponatremia as a marker of disease severity. When serum sodium concentrations were measured over time in a single patient (Fig. 2), hyponatremia was associated with decreased preload (digestive hemorrhage) or sepsis/inflammation (bacterial peritonitis). Recurrent ascites with hyponatremia frequently remains of unknown origin. Thus, besides rare neurological disorders induced by rapid modifications of serum sodium concentration, hyponatremia is likely to be a surrogate marker of either decreased preload, aggravation of cardiomyopathy, aggravation of liver disease (increased splanchnic vasodilatation), or occurrence of a septic-like syndrome through arterial underfilling. Guidelines have been published to treat episodes of hyponatremia in cirrhotic patients [34]. However, treatment of acute complications of cirrhosis and OLT are likely to be the best therapies when hyponatremia occurs [35].

Finally, the exact mechanism of hyponatremia correction during OLT is yet to be elucidated. In our study, normalization of serum sodium concentrations within the surgical period was unrelated to the systemic vascular resistance that remain unchanged in Child_C patients during the perioperative period. Although,

portal blood flow immediately increases with graft placement, correction of the splanchnic arterial vasodilatation is usually observed only within 3 to 6 months after OLT [36]. The systemic vascular resistance is unlikely to be reflected by the stimulation of arterial baroreceptors by arterial underfilling as previously shown by Rector et al. [37]. RW Schrier [1, 4] emphasizes that arterial underfilling should be assessed by the release of neurohormones. In the ANH phase of OLT, serum renin activity and concentrations of epinephrine, vasopressin, and pro-BNP increased similarly in both Child_{AB} and Child_C patients (Table 4) as previously described [38]. However, the unstable perioperative conditions associated with a high neurohormonal response precludes correlating the normalization of serum sodium concentration to a decrease hormone release. Eyraud et al. have already shown in 2002 [39] that, in patients with normal liver function who had major hepatic resection with portal triad clamping and occlusion of the inferior vena cava below and above the liver, the sudden drop in venous return enhances the neurohormonal response to sustain the systemic hemodynamics. After unclamping, endogenous catecholamines, vasopressin, renin and atrial natriuretic peptide return to baseline values within five minutes. These observations suggest that this acute neurohormonal response, which is similarly observed in our study, do not solely explain the progressive normalization of sodium levels observed after OLT.

Interestingly, Cystatin-C values were moderately but significantly higher in the Child_C group 24 hours after OLT. This increase is consistent with recent studies showing that Cystatin-C is a more sensitive indicator for renal impairment in cirrhotic patients than serum creatinine and creatinine clearance [40]. Moreover, higher values of Cystatin-C were correlated with a more severe cirrhotic disease [41] and has been shown to be an independent predictor of post OLT survival [42]. Thus, Cystatin-C measurement might be of interest for early detection of kidney disease and as so, help prevent renal related complications in cirrhotic patients. In addition, the sensitivity of Cystatin-C for early detection of kidney disease in cirrhotic patients, its correlation with the severity of the disease and its prediction value for post OLT mortality could place the cystatin-C as an interesting factor in prioritizing patients in the OLT waiting list and should be further studied.

Our study has significant limitations. The number of patients was limited and the number of patients with a very low natremia (only 3 out of 27 patients had sodium levels < 130 mmol/l) even smaller, the sample size however, correlates to our institution's annual average liver transplantations. Furthermore, the choice of using the Child-Pugh classification to assess severity of cirrhosis could be a matter of debate. Since the MELD score was adopted in 2002 to allocate priority to candidates, the mortality on the waiting list has decreased. The MELD score predicts the survival for patients with cirrhosis more accurately than the Child score. Interestingly, in patients with hyponatremia, the MELD-Na score might further decrease the 90-days mortality on the waiting list [14]. However, to assess the severity of cirrhosis in our study, we chose the Child-Pugh score that reflects clinical symptoms (encephalopathy and ascites) better than the MELD score, which is based on the logarithmic transformation of bilirubin, creatinine, and INR.

Conclusions

In summary, hyponatremia at listing is now recognized as an independent factor of mortality within 90 days after OLT. Moreover, in OLT candidates with cirrhosis, episodes of hyponatremia are likely to be associated with disease complications and the importance of serial determination should be investigated. A score including sodium concentration variations may be an interesting parameter to consider before OLT. Interestingly, in our study, hyponatremia was rapidly corrected after successful liver transplantation without observed complications. Short- and long-term clinical outcomes and prognostic value of this correction in the post-operative period remains to be better understood. Finally, the fact that sodium levels remain stable after post-operative correction despite a persistent splanchnic vasodilatation suggests that probably other mechanisms are implicated in hyponatremia associated with cirrhosis and further studies on the subject would be of interest.

Declarations

Ethics Statement

The ethics committee of our institution (Hôpitaux Universitaires de Genève, Geneva, Switzerland) approved the protocol and written informed consent was obtained from each patient at the time of inclusion in the waiting list.

The study has been registered in the ISRCTN register (N° 43452247). Details can be found at <https://www.isrctn.com/ISRCTN43452247?q=43452247&filters=&sort=&offset=1&totalResults=1&page=1&pageSize=10&searchType=basic-search>

Consent for publication

All authors have approved the manuscript and agree with its submission.

Competing interests

None declared.

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Authors' Contributions

Dr. Ido Zamberg – Wrote the manuscript, took part in the analysis of results and literature review.

Prof. Eduardo Schiffer – Team leader and main investigator, wrote the manuscript, performed statistical analysis.

Dr. Julien Maillard – Participated in writing first draft, data collection and critically revised the manuscript.

Dr. Simon Tomala - Participated in writing first draft and critically revised the manuscript.

Dr. Benjamin Assouline – Critically revised the manuscript and took part in statistical analysis.

Dr. Thomas Mavrakanas - Critically revised the manuscript and performed statistical analysis.

Dr. Axel Andres – Participated in patients' inclusion, critically revised the manuscript.

Dr. GleicyKeli-Bracelos – Participated in patients' inclusion, critically revised the manuscript.

Dr. FlorenceAldenkortt – Participated in patients' inclusion, critically revised the manuscript.

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Figures

Figure 1

Plasma sodium concentration [mmol/l] at the PREOLT period (A), during the perioperative period (B), 7 days (C), and 6 months (D) after OLT. * $p < 0.002$ with MannWhitney comparison between both groups. ** $p < 0.02$ for interaction between time and Child with MANOVA with repeated mesures analysis. In panel B, closed squares are ChildAB patients and open squares are ChildC patients. Perioperative periods are: anesthesia (ANE), anhepatic (ANH), 1 hour (POST_{1h}) and 24 hours (POST_{24h}) after hepatic reperfusion.

Figure 2

Serial determination of plasma sodium concentrations in a single patient from the ChildC group. The PREOLT value of plasma sodium concentration was 136 mmol/L (arrow).

Figure 3

Mean arterial pressure [mmHg], cardiac index [l/min/m²], systemic vascular resistance [dynes . sec . cm⁻⁵ per m²], and heart rate [beats per min] during the perioperative period: anesthesia (ANE), anhepatic period (ANH), 1 hour (POST_{1h}) and 24 hours (POST_{24h}) after hepatic reperfusion. Closed squares are ChildAB patients and open squares are ChildC patients.

Figure 4

Pathophysiology of hyponatremia during the complications of cirrhosis. Sympathetic nervous system (SNS); Renin angiotensin aldosterone system (RAAS); Arginine vasopressin (AVP).