Renal Failure

ISSN: 0886-022X (Print) 1525-6049 (Online) Journal homepage: informahealthcare.com/journals/irnf20

Serum sodium shift in hyponatremic patients undergoing liver transplantation: a retrospective cohort study

Adam Romanovsky, Luciano C.P. Azevedo, Glenda Meeberg, Rayna Zibdawi, David Bigam & Sean M. Bagshaw

To cite this article: Adam Romanovsky, Luciano C.P. Azevedo, Glenda Meeberg, Rayna Zibdawi, David Bigam & Sean M. Bagshaw (2015) Serum sodium shift in hyponatremic patients undergoing liver transplantation: a retrospective cohort study, Renal Failure, 37:1, 37-44, DOI: 10.3109/0886022X.2014.975102

To link to this article: https://doi.org/10.3109/0886022X.2014.975102

Published online: 27 Oct 2014.

RENAL FAILURE

http://informahealthcare.com/rnf
ISSN: 0886-022X (print), 1525-6049 (electronic)

Ren Fail, 2015; 37(1): 37–44
 DOI: 10.3109/0886022X.2014.975102

informa
healthcare

CLINICAL STUDY

Serum sodium shift in hyponatremic patients undergoing liver transplantation: a retrospective cohort study

Adam Romanovsky[1,2], Luciano C.P. Azevedo[1], Glenda Meeberg[3], Rayna Zibdawi[1], David Bigam[3], and Sean M. Bagshaw[1]

[1]*Division of Critical Care Medicine, University of Alberta, Edmonton, Canada,* [2]*Division of Nephrology, University of Alberta, Edmonton, Canada, and* [3]*Department of Surgery, University of Alberta, Edmonton, Canada*

Abstract

Introduction: We aimed to describe the pre-operative incidence of hyponatremia in patients undergoing liver transplantation (LTx), as well as the rate and consequences of rapid peri-operative sodium rises in these patients. *Methods*: This was a retrospective before and after observational study performed at a University-affiliated LTx center between January 2007 and June 2013. The primary exposure was pre-operative hyponatremia, defined as a serum sodium (SNa) <133 mmol/L. The primary outcome was occurrence of a rapid SNa shift, defined as ≥10 mmol/L in the first 24 h following LTx. The rates of rapid peri-operative SNa shift were compared before and after a focused quality assurance (QA) initiative performed in July 2009. *Results*: Of 366 LTx, 69 (18.9%) had pre-operative hyponatremia, 6 (8.7%) of whom had a rapid rise in serum sodium (SNa). Rapid rise was associated with a greater intra-operative positive fluid balance ($p < 0.001$) and use of intra-operative continuous renal replacement therapy (CRRT) ($p = 0.017$). A rapid rise in SNa was associated with more neurological investigations in the post-transplant period (brain computed tomography, electroencephalogram, swallow studies), increased neurological deficits ($p = 0.006$), more abnormal swallowing assessments ($p = 0.003$), a tendency for more neurology consultations ($p = 0.058$), increased discharge to a rehabilitation or long-term care facility ($p < 0.001$), and increased 6-month mortality ($p < 0.001$). Following a QA initiative, rapid peri-operative rises in SNa among hyponatremic patients was significantly reduced (20% vs. 0%, $p < 0.003$). *Conclusion*: Pre-operative hyponatremia and rapid peri-operative SNa shifts are associated with a more complicated post-operative course and worse outcomes following LTx. Increased education and awareness, along with process changes, such as standardizing CRRT prescription, can reduce iatrogenic rapid peri-operative shifts in SNa.

Keywords

Central pontine myelinolysis, continuous renal replacement therapy, hyponatremia, liver transplant, osmotic demyelination

History

Received 30 March 2014
Revised 26 August 2014
Accepted 26 September 2014
Published online 27 October 2014

Introduction

Rapid correction of serum sodium (SNa) in patients with chronic hyponatremia may pre-dispose to osmotic demyelination syndrome (ODS) due to the compensatory extracellular movement of electrolytes and organic osmolytes.[1–5] Both animal and human data showed that the absolute rise in SNa within a 24- or 48-hour period is highly predictive for the development of ODS.[4–7] The exact margin by which SNa can be safely raised in a day remains controversial, but the literature supports an increase of not greater than 8–12 mmol/L per 24 h or 18 mmol/L over 48 h.[7,8]

Many cirrhotic patients develop hyponatremia and more than 30% are hyponatremic at the time of liver transplantation (LTx).[9,10] Hyponatremia is mediated, in part, by elevated circulating levels of arginine vasopressin due to vasodilatation-induced reductions in effective circulating volume.[11–13] These patients are therefore at risk of ODS with any intervention that contributes to a rapid elevation in SNa. Post-operative ODS can be heterogeneous in presentation and difficult to diagnose; however, confirmation correlates with worse clinical outcome and long-term disability.[14]

Several studies have shown hyponatremia to be a poor prognostic indicator for cirrhotic patients receiving LTx.[9,15–18] Yun et al.[9] found that pre-operative hyponatremia is associated with an increased risk for post-operative ODS, along with prolonged stay in both ICU and hospital. On the other hand, few studies have focused on the rate of peri-operative SNa correction and its relationship with post-operative neurologic outcomes.[18–20] Yu et al.[19] demonstrated a 3.5% incidence of ODS post-LTx that was associated with an increased rate of SNa correction.

Thus, we hypothesized that patients with pre-operative hyponatremia would be at an increased risk for rapid SNa shift in the immediate post-operative period and that this

Address correspondence to Dr Sean M. Bagshaw, Division of Critical Care Medicine, University of Alberta, 2-124E Clinical Sciences Building, 8440-112 Street, Edmonton, Alberta T6G2B7, Canada. Tel: (780) 492-8311; Fax: (780) 492-1500; E-mail: bagshaw@ualberta.ca

would translate into a more complicated clinical course and worse post-LTx outcome. Accordingly, our objectives were: (1) To describe the incidence of and rate of increase in SNa in hyponatremic patients following LTx; (2) To describe the clinical and/or therapeutic factors associated with rapid increases in SNa following LTx; (3) To describe the association between rapid increases in SNa and clinical outcomes; and (4) To evaluate the impact of a focused quality assurance initiative to reduce the risk of rapid peri-operative SNa shift following LTx.

Methods

The study protocol was approved by the Health Research Ethics Board at the University of Alberta prior to commencement. Due to its retrospective observational design the need for informed consent was waived.

Study design and setting

The study was a retrospective observational before and after cohort study of patients undergoing liver transplantation (LTx) at the University of Alberta Hospital between 1 January 2007 and 20 June 2013. The University of Alberta Hospital Liver Transplant Program was started in 1989 and now performs approximately 70 liver transplants annually.

Study population

Patients were included if they were $\geq$18 years and had a documented pre-operative SNa $<$133 mmol/L within 24 h of LTx. This threshold for hyponatremia was chosen, as it is the lower limit of normal in our laboratory. If patients had multiple SNa measures during this period, the measure nearest to the start of surgery was used. SNa measurements were captured for the subsequent 48 h. The post-operative change in SNa during the first 24 and 48 h was determined. A rapid rise in post-operative SNa was defined as a change in SNa $\geq$10 mmol/L in the first 24 h.[8]

Study protocol

All patients who received a LTx during the study period were identified by review of the University of Alberta Hospital Liver Transplant Program database (Organ Transplant Tracking Record [OTTR], HKS Medical Information Systems, Omaha, NE).

Each eligible patient underwent a review of their medical record and ascertainment of clinical outcomes. Data captured for each patient included demographics (i.e. age, sex, co-morbidities, pre-LTx disposition), liver disease details (i.e. liver diagnoses, pre-operative complications), acute physiology/laboratory parameters (i.e. 24 h prior, intra- and post-operatively), and details of surgery. Intra-operative and post-operative data captured included use of vasopressors, fluid balance, diuretic use, and need for renal replacement therapy (RRT). Outcome data ascertained included duration of mechanical ventilation, re-intubation rate, need for neuroimaging or swallowing studies, mental status changes, neurological deficits or complications (as specifically described in the medical record), as well as ICU and hospital lengths of stay, mortality, and discharge location.

Study definitions

Severity of liver disease was assessed by the calculation of the unadjusted Model for End-Stage Liver Disease (MELD) score.[21] The MELD score used was the composite score calculated immediately prior to LTx. The presence of comorbidities was characterized and quantified by the Charlson co-morbidity index.[22]

Data sources

All data were collected on standardized case report forms. Data were extracted from the Liver Transplant Program database and through individual medical record review. The Liver Transplant Program database was interrogated for peri-operative data. Individual medical record review was conducted for data on SNa, details of pre-, intra-, and post-operative clinical factors and outcomes.

Quality assurance/improvement review

In July 2009, a quality assurance/improvement review of the peri-operative management of LTx patients with pre-operative hyponatremia was undertaken. Data from before and after the review were analyzed and compared. From this review, several initiatives to improve awareness of the potential iatrogenic complications related to rapid peri-operative sodium shifts were undertaken along with interventions to mitigate excessive peri-operative SNa shift. The implementation phase of the QA review included engaging stakeholders through presentations, the introduction of standardized documentation and the availability of a consultative service. Presentations on the risks and management of peri-operative hyponatremia were held in the form of rounds and educational sessions across inter-disciplinary settings over the subsequent 6 months, including liver transplant surgeons, anesthesiologists and critical care. We immediately developed and introduced standardized orders for the set up and management of intra-operative CRRT during LT, specifically addressing modification of replacement fluid to mitigate excessive iatrogenic rises in SNa if pre-operative hyponatremia was evident. Finally, for patients with pre-operative hyponatremia, we also immediately recommended patients be reviewed in consultation with an expert in hyponatremia management who is also familiar with LTx (i.e. experts were among three experienced intensivists with training in critical care nephrology).

Statistical analysis

Analysis was performed using Stata 13 (Stata Corp, College Station, TX). In the event of missing data values, data were not replaced or estimated. For analysis of the primary objective, incidence of peri-operative rapid SNa change, descriptive statistics were used. The absolute and relative changes to peri-operative SNa were reported for normally or near normally distributed variables as means with standard deviations (SD) and compared by Student's *t*-test and for non-normally distributed continuous data as medians and P25–P75 and compared by Mann–Whitney *U*-test. Post-operative SNa $\geq$10 mmol/L were reported as proportions and compared using Fisher's exact test. A p-value of <0.05 was considered statistically significant for all comparisons.

Results

A total of 366 patients received LTx during the study period, of which 69 (18.9%) had a pre-operative SNa <133 mmol/L. Of these patients, 6 (8.7%) had a rapid correction of SNa within the first 24 post-operative hours. This represented 1.6% of all LTx performed during the study period. All 6 patients who had a rapid correction of SNa had either documented chronic hyponatremia or hyponatremia of unknown duration at the time of LTx.

Analysis according to sodium alterations in the peri-operative period

LTx patients with a rapid SNa shift were more likely to be hospitalized prior to surgery (83.3% vs. 29.2%, $p = 0.02$) (Table 1). The Charlson comorbidity score was also greater in hyponatremic patients with a rapid SNa shift as compared to those without rapid shift ($p < 0.001$). There were no other significant differences between the two groups.

Pre-operative SNa in the rapid correction group was significantly lower than the control group (129 vs. 126 mmol/L, $p = 0.047$). There were no differences between the rapid correction and control group in pre-operative vasopressor use, RRT, diuretics, or corticosteroid use.

The change in SNa in the first 24 h was significantly higher for the rapid correction group (mean 12.8, SD 1.9, mmol/L) as compared to controls (mean 3.3, SD 2.9) ($p < 0.001$) (Table 2). After 48 h, the mean change in SNa in the rapid correction group was also significantly higher (mean 10.5, SD 1.3) compared to the control group (mean 4.9, SD 3.6 mmol/L) ($p < 0.001$). Those with a rapid shift had a greater intra-operative fluid balance compared with controls. Rapid SNa shift was more likely in those receiving intra-operative CRRT compared with controls. There were no differences between the rapid correction and controls in post-operative use of vasopressors, RRT, or diuretics. Corticosteroids were more commonly used in the rapid correction group.

There was no statistical differences in post-operative duration of mechanical ventilation, need for re-intubation, or difficulty in the weaning process (Table 3). On the other hand, brain-computed tomography, electroencephalogram, and swallow studies were more commonly performed in patients with rapid SNa correction as compared to controls. Moreover, these patients had more abnormal results on the swallowing tests and had more neurological deficits. These data may partially explain the non-significant trend toward more neurological consultations in the rapid shift group. There was a greater likelihood of discharge to a rehabilitation/long-term care facility and 6-mortality in the rapid correction group compared with controls.

Subgroup analysis following quality assurance review

Table 4 identifies the clinical characteristics of the groups before and after the QA review. In the post-review period, patients showed a trend for higher MELD score compared with the pre-review period. No other differences were observed regarding the characteristics of both groups. There were no clinically significant differences in acute physiology between the pre- and post-review periods (Table 4).

Table 5 describes the peri-operative changes to SNa and interventions received before and after the QA review. Despite similar baseline SNa values, those undergoing LTx in the post-review period showed lower peri-operative SNa shift at 24 h and none had a shift > 10 mmol/L in the first 24 h compared to 6 in the pre-review period ($p = 0.003$). In addition, post-review patients had lower intra-operative fluid accumulation and received less corticosteroids compared with the pre-review group.

Clinical investigations and outcomes are shown in Table 6. Though not statistically significant, patients receiving LTx in the post-review period showed trends for fewer neurologic deficits and neurology consultations. Moreover, post-review patients showed a lower mortality at 6 months ($p = 0.043$).

Discussion

We conducted a retrospective surveillance of hyponatremic patients receiving liver transplantation to describe the incidence of rapid peri-operative SNa shift and describe the clinical and therapeutic factors and outcomes associated with rapid SNa shifts. We also evaluated the impact of a quality assurance review and implementation of recommendations on the occurrence of rapid peri-operative SNa shifts.

Table 1. Summary of baseline characteristics and pre-operative physiology, laboratory values and interventions.

Variables	Total ($n = 69$)	SNa < 10 mmol/L ($n = 63$)	SNa ≥10 mmol/L ($n = 6$)	p-Value
Age at time of LT (mean [SD]) (years)	53.3 (10.3)	53 (10.5)	57 (7.8)	0.369
Male sex (%)	44 (64)	40 (63)	4 (66)	0.916
MELD Score (mean [SD])	24.2 (8.5)	24.2 (8.6)	23.5 (8.7)	0.834
Indication for Lx transplantation*				
Hepatitis C virus	26 (38)	25 (40)	1 (17)	0.255
Alcoholic cirrhosis	16 (23)	14 (22)	2 (33)	0.553
Hepatocellular carcinoma	14 (20)	13 (21)	1 (17)	0.804
Other indications	32 (46)	29 (46)	3 (50)	0.880
Disposition at time of LT (%)				0.02
Home	13 (43.3)	13 (54.2)	0 (0)	
Hospitalized	12 (40.0)	7 (29.2)	5 (83.3)	
ICU	5 (16.7)	4 (16.7)	1 (16.7)	
Living donor (%)	11 (16)	10 (16)	1 (17)	0.960

Notes: *More than one indication may apply.
LT = liver transplant; MELD = model for end-stage liver disease; ICU = intensive care unit; RRT = renal replacement therapy.

Table 2. Details of peri-operative serum sodium shift, and intra/post-operative interventions.

Variables	Total ($n = 69$)	SNa <10 mmol/L ($n = 63$)	SNa ≥ 10 mmol/L ($n = 6$)	p-Value
Pre-operative sodium (SNa) (mean [SD]) (mmol/L)	129 (3)	129 (2)	126 (4)	0.047
ΔSNa at 24 h (mean [SD]) (mmol/L)	4.1 (3.9)	3.3 (2.9)	12.8 (1.9)	<0.001
Post-operative SNa at 24 h (mean [SD]) (mmol/L)	133 (4)	132 (4)	139 (4)	<0.001
ΔSNa at 48 h (mean [SD]) (mmol/L)	5.4 (3.8)	4.9 (3.6)	10.5 (1.3)	<0.001
Post-operative SNa at 48 h (mean [SD]) (mmol/L)	134 (4)	134 (4)	137 (4)	0.056
Increase in SNa >10 mmol/L at 48 h (%)	8 (12)	3 (5)	5 (83)	<0.001
Operative duration (mean [SD]) (min)	406 (142)	408 (134)	389 (224)	0.761
Intra-operative fluid balance (med [P25–P75]) (L)	5.6 (4.0–7.75)	5.2 (3.8–7.2)	9.8 (8.1–26.3)	<0.001
Post-operative fluid balance at 24 h (med [P25–P75]) (L)	3.0 (1.2–5.2)	2.5 (0.9–5.1)	4.9 (3.5–7.2)	0.077
Intra-operative CRRT (%)	11 (16)	8 (13)	3 (50)	0.017
Post-operative RRT (%)	12 (17)	10 (16)	2 (33)	0.281
Intra-operative vasopressors (%)				
Any (%)	69 (100)	63 (100)	6 (100)	–
Vasopressin (%)	54 (78)	49 (78)	5 (83)	0.753
Post-operative vasopressors (%)				
Any (%)	43 (62)	39 (62)	4 (67)	0.818
Vasopressin (%)	27 (39)	23 (37)	4 (67)	0.148
Post-operative corticosteroids (%)	11 (16)	8 (13)	3 (50)	0.017
Post-operative diuretics (%)	16 (23)	15 (24)	1 (17)	0.692

Notes: SNa = serum sodium; CRRT = continuous renal replacement therapy; RRT = renal replacement therapy.

Table 3. Summary of clinical outcomes.

Variables	Total ($n = 69$)	SNa <10 mmol/L ($n = 63$)	SNa ≥10 mmol/L ($n = 6$)	p-Value
Duration of MV (med [P25–P75]) (days)	2 (1–3)	1 (1–3)	3 (1–33)	0.189
Re-intubation required (%)	16 (23)	13 (21)	3 (50)	0.109
Difficult to wean from mechanical ventilation (%)	14 (20)	12 (19)	2 (33)	0.406
Tracheostomy (%)	10 (14)	8 (13)	2 (33)	0.170
ICU length of stay (med [P25–P75]) (days)	4 (2–8)	5 (2–12)	8 (3–71)	0.337
MET activation (%)	15 (22)	13 (21)	2 (33)	0.471
ICU re-admission (%)	15 (22)	13 (21)	2 (33)	0.471
Brain CT (%)	16 (23)	12 (19)	4 (63)	0.008
Brain MRI (%)	15 (22)	13 (21)	2 (33)	0.471
EEG (%)	6 (9)	5 (8)	2 (33)	0.049
Abnormal mental status (%)	24 (35)	21 (33)	3 (50)	0.416
Confusion	14 (20)	13 (21)	1 (17)	
Delirium	7 (10)	6 (10)	1 (17)	
Altered level of conscience	3 (4)	2 (3)	1 (17)	
Neurological deficits§ (%)	9 (13)	6 (10)	3 (50)	0.006
Neurology consultation (%)	14 (20)	11 (17)	3 (50)	0.058
Speech-pathology consultation (swallow study) (%)	16 (23)	13 (21)	3 (50)	0.003
Normal (%)	9 (13)	9 (15)	0 (0)	
Abnormal (%)	7 (10)	4 (6)	3 (50)	
Hospital length of stay (med [P25–P75]) (days)	30 (21–46)	30 (21–46)	32 (21–127)	0.424
Discharge location (%)				<0.001
Home	58 (84)	55 (87)	3 (50)	
Death	1 (1)	0 (0)	1 (17)	
Other hospital	5 (7)	5 (8)	0 (0)	
Rehab/long-term care	5 (7)	3 (5)	2 (33)	
6-month mortality (%)	3 (4)	1 (2)	2 (33)	<0.001

Notes: EEG = electroencephalogram; CT = computerized tomography; MRI = magnetic resonance imaging; ICU = intensive care unit; MET = medical emergency team; MV = mechanical ventilation.
§Deficits included: focal neurologic deficits; seizure.

Key findings

We found that 18.9% of patients were hyponatremic prior to LTx. We also found that 8.7% of these patients had a shift in SNa of ≥10 mmol/L in 24 h following surgery; a degree of change known to be associated with ODS.[5,7] A rapid correction in SNa was associated with a greater intra-operative positive fluid balance and use of intra-operative CRRT. Patients with a rapid correction were more likely to require neurological tests in the post-transplant phase, had more neurological deficits, and abnormal findings on formal swallowing assessments. Rapid peri-operative SNa shifts were also associated with discharge to dependent living and lower survival. Moreover, we found an inter-disciplinary quality assurance review to increase awareness and implement recommendations significantly reduced the occurrence of iatrogenic peri-operative rapid shifts in SNa. Despite similar severity of pre-operative illness, those receiving LTx in the

Table 4. Summary of preoperative acute physiology and laboratory values, divided according to before and after QA implementation.

Characteristic	Overall ($n = 69$)	Before QA Review ($n = 30$)	After QA Review ($n = 39$)	p-Value
MELD Score (mean [SD])	24.2 (8.5)	22.6 (8.4)	25.4 (8.5)	0.172
Temperature (mean [SD]) (degree Celsius)	35.9 (0.6)	36.2 (0.6)	35.8 (0.6)	0.012
Heart rate (mean [SD]) (/min)	82.0 (12.5)	81.1 (13.8)	82.7 (11.1)	0.593
Mean arterial pressure (mean [SD]) (mmHg)	83.7 (11.2)	82.1 (8.4)	85.0 (12.9)	0.290
CVP (mean [SD]) (mmHg)	12.2 (5.3)	11.6 (4.9)	12.7 (5.6)	0.381
Hemoglobin (mean [SD]) (g/L)	104 (18)	110 (20)	100 (17)	0.025
White cell count (med [P25–P75]) (10^9 cells/mL)	5.3 (4.3–7.6)	6.2 (4.5–9.2)	5.1 (3.9–6.3)	0.087
Platelets (mean [SD]) (10^9 cells/mL)	93 (76)	105 (75)	85 (77)	0.301
Bilirubin (med [P25-P75]) (μmol/L)	94 (47–306)	89 (53–372)	110 (35–288)	0.545
INR (mean [SD])	1.8 (0.6)	1.7 (0.5)	1.9 (0.8)	0.091
Albumin (mean [SD]) (μmol/L)	31.6 (7)	32.3 (8)	31.1 (6)	0.487
Sodium (SNa) (mean [SD]) (mmol/L)	129 (3)	129 (3)	128 (3)	0.643
Serum creatinine (mean [SD]) (μmol/L)	93 (49)	100 (46)	87 (52)	0.334
Pre-operative vasopressors (%)	3 (4)	1 (3)	2(5)	–
Pre-operative RRT (%)	10 (14)	3 (10)	7 (17)	0.352
Pre-operative corticosteroids (%)	6 (8)	4 (13)	2 (5)	0.230
Pre-operative diuretic therapy (%)	49 (71)	24 (80)	25 (64)	0.149

Notes: QA = quality assurance; SD = standard deviation; MELD = model for end-stage liver disease; ICU = intensive care unit; CVP = central venous pressure; INR = international normalized ratio; RRT = renal replacement therapy.

Table 5. Details of peri-operative serum sodium shift, and intra/post-operative treatments, divided according to before and after QA implementation.

Characteristic	Overall ($n = 69$)	Before QA review ($n = 30$)	After QA review ($n = 39$)	p-Value
Pre-operative sodium (SNa) (mean [SD]) (mmol/L)	129 (3)	129 (3)	128 (3)	0.643
Δ SNa at 24 h (mean [SD]) (mmol/L)	4.1 (3.9)	5.3 (4.8)	3.3 (2.8)	0.036
Post-operative SNa at 24 h (mean [SD]) (mmol/L)	133 (4)	134 (5)	132 (4)	0.135
Increase in SNa >10 mmol/L at 24 h (%)	6 (9)	6 (20)	0 (0)	0.003
Δ SNa at 48 h (mean [SD]) (mmol/L)	5.3 (3.8)	5.9 (4.3)	4.9 (3.4)	0.310
Post-operative SNa at 48 h (mean [SD]) (mmol/L)	134 (4)	135 (5)	134 (3)	0.509
Increase in SNa >10 mmol/L at 48 h (%)	8 (12)	5 (17)	3 (8)	0.248
Operative duration (mean [SD]) (min)	406 (142)	403 (184)	409 (102)	0.861
Intra-operative fluid balance (med [P25–P75]) (L)	5.6 (4.0–7.75)	6.4 (4.6–7.9)	5.2 (3.3–8.0)	0.020
Post-operative fluid balance at 24 h (med [P25–P75]) (L)	3.0 (1.2–5.2)	2.9 (0.8–5.6)	3.4 (1.6–4.8)	0.799
Post-operative fluid balance at 48 h (med [P25–P75]) (L)	2.8 (1.2–4.0)	2.7 (0.8–4.0)	3.0 (1.5–4.2)	0.934
Intra-operative CRRT (%)	11 (16)	5 (17)	6 (15)	0.885
Post-operative RRT (%)	12 (17)	4 (13.3)	8 (20)	0.435
Intra-operative vasopressors (%)				
Any (%)	69 (100)	30 (100)	39 (100)	–
Vasopressin (%)	54 (78)	22 (73)	32 (82)	0.384
Post-operative vasopressors (%)				
Any (%)	41 (59)	16 (53)	27 (69)	0.177
Vasopressin (%)	27 (39)	9 (30)	18(46)	0.173
Post-operative diuretics (%)	16 (23)	7 (23)	9 (23)	0.980

Notes: QA = quality assurance; SNa = serum sodium; SD = standard deviation; CRRT = continuous renal replacement therapy; RRT = renal replacement therapy.

post-review period showed trends for fewer neurologic deficits and neurology consultations along with improved 6-month survival.

Interpretation and context with prior literature

The incidence of pre-operative hyponatremia in our study is consistent with the rates described in prior studies. When defined as a SNa <135 mmol/L, two large observational studies described an incidence of pre-operative hyponatremia in the range of 31.3–32.4%.[9,10] The lower incidence in our study is likely attributable to defining hyponatremia by a lower threshold (SNa <133 mmol/L). Not only have prior data shown that pre-operative hyponatremia is relatively common and a negative prognostic factor, it has also been associated with an increased iatrogenic risk of post-operative ODS.[15,17,19,23–26] In a 10-year retrospective surveillance of 2175 patients undergoing LTx, Yun et al.[9] found the development of post-operative ODS occurred in 0.5% of patients and was correlated with a lower pre-operative SNa (129 vs. 136 mmol/L). Previous studies also linked pre-operative hyponatremia to an increased risk of rapid SNa shift and undesired complications.[9,20] One study found patients with a pre-operative SNa <130 mmol/L were more likely to undergo a rapid intra-operative increases in SNa.[27] Boon et al.[28] described five cases of previously undiagnosed myelinolysis among 50 post-mortem examinations of patients who died following LTx. Four of these patients had a rapid peri-operative increase in SNa, of whom three had a pre-operative SNa <133 mmol/L.[28] Similarly, Singh et al.[29] showed that patients with myelinolysis had marked peri-operative variations in SNa (>15 mmol/L).

Table 6. Summary of clinical outcomes, divided according to before and after QA implementation.

Characteristic	Overall ($n = 69$)	Before QA review ($n = 30$)	After QA review ($n = 39$)	p-Value
Duration of MV (med [P25–P75]) (days)	2 (1–3)	2 (1–4)	1 (1–3)	0.784
Re-intubation required (%)	16 (23)	5 (16)	11 (28)	0.236
Difficult to wean from mechanical ventilation (%)	14 (20)	4 (13)	10 (25)	0.208
Tracheostomy (%)	10 (14)	6 (20)	4 (10)	0.254
ICU length of stay (med [P25–P75]) (days)	4 (2–8)	4 (2–12)	4 (2–7)	0.651
MET activation (%)	15 (22)	5 (16)	10 (25)	0.370
ICU re-admission (%)	15 (22)	5 (16)	10 (25)	0.370
Brain CT (%)	16 (23)	9 (30)	7 (18)	0.240
Brain MRI (%)	15 (22)	5 (16)	10 (25)	0.370
EEG (%)	6 (9)	4 (13)	2 (5)	0.442
Abnormal mental status (%)	24 (35)	9 (30)	15 (38)	0.464
Confusion	14 (20)	7 (23)	7 (18)	
Delirium	7 (10)	1 (3)	6 (15)	
Altered level of conscience	3 (4)	1 (3)	2 (5)	
Neurological deficits§ (%)	9 (13)	6 (20)	3 (8)	0.156
Neurology consultation (%)	14 (20)	9 (30)	5 (13)	0.079
Speech-pathology consultation (swallow study) (%)	16 (23)	8 (27)	8 (21)	0.261
Abnormal (%)	7 (10)	5 (17)	2 (5)	
Hospital length of stay (med [P25–P75]) (days)	30 (21–46)	31 (23–50)	30 (17–43)	0.482
Discharge location (%)				0.125
Home	58 (84)	26 (86)	32 (82)	
Death	1 (1)	1 (3)	0 (0)	
Other hospital	5 (7)	0 (0)	5 (13)	
Rehab/long-term care	5 (7)	3 (10)	2 (5)	
6-month mortality (%)	3 (4)	3 (10)	0 (0)	0.043

Notes: QA = quality assurance; EEG = electroencephalogram; CT = computerized tomography; MRI = magnetic resonance imaging; ICU = intensive care unit; MET = medical emergency team; MV = mechanical ventilation.
§Deficits included: focal neurologic deficits; seizure.

Lee et al.,[20] evaluating 11 patients with central pontine and extrapontine myelinolysis after LTx, identified an increased rate of SNa correction in these patients as compared to the control group (14.5 vs. 4.2 mEq/L). In a recent study of 512 patients undergoing LTx, Lee et al.[18] demonstrated that correction of hyponatremia at a rate higher than 12 mmol/L/24 h was an independent risk factor for post-operative neurologic complications.

While none of the patients in our study had clinical or radiographically confirmed demyelination, the diagnosis of ODS following LTx is challenging, and it is plausible that the diagnosis was missed.[28] Although ODS may classically present with quadriparesis, the clinical manifestations following LTx can be highly variable.[20,30] For example, in a series of 12 patients with ODS confirmed by either neuro-imaging or brain autopsy, Odier et al.[31] described a range of clinical manifestations including dysphagia, alterations to consciousness, cerebellar dysfunction, and seizures. Similarly in our study, we chose a wide array of potential neurologic manifestations that may have resulted from subclinical pontine or extra-pontine myelinolysis. The observed higher incidence of neurologic testing and consultations along with more abnormal swallowing studies and neurologic deficits may all represent such subtle manifestations.

LTx is a complex procedure with a significant risk of bleeding and evaporative fluid loss. To maintain intravascular volume, ''isotonic'' crystalloid is administered along with blood transfusions as necessary. In our study, all patients received crystalloid with a [Na] of 130–154 mmol/L. This is not only hypertonic when compared with the SNa of the hyponatremic patient, but is particularly high in [Na] considering that many of these patients may have been excreting urine with a low [Na]. The finding that the rapid correction group had greater intra-operative fluid balance suggests that this excess [Na] load may have contributed to the observed rapid rise in SNa. These results are consistent with those of Lee et al.,[20] who correlated greater intra-operative crystalloid and blood transfusions with an increased risk of developing ODS. Higher volume of crystalloid infusion may also have resulted in a more potent inhibition of arginine vasopressin, leading to excretion of dilute urine with a resultant increase in SNa. In addition, resuscitation with both albumin and concentrated sodium bicarbonate ($NaHCO_3$) may also contribute to an increase in delivered [Na].

Implications for health policy

Of particular interest is the association between a rapid rise in SNa and the use of intra-operative continuous renal replacement therapy (CRRT). The typical [Na] concentration of commercially available replacement/dialysate fluid, and that used at our institution is 140 mmol/L. Exposing hyponatremic patients to these fluids will therefore lead to an increase in SNa. The risk of a rapid SNa shift becomes greater relative to the severity of hyponatremia, as the difference in serum and replacement fluid [Na] widens. In addition, a high total effluent dose will also contribute to the SNa more rapidly approaching the [Na] replacement/dialysate fluid. Such increases in dose intensity are often undertaken to more effectively maintain potassium homeostasis and serum pH. While replacement/dialysate fluids may be altered to reduce the [Na] concentration, this can be complicated and was not routinely performed in any of the patients in our study prior

to the QA review. Moreover, the addition of supplemental $NaHCO_3$ (added to replacement or dialysate) can further predispose to risk of a rapid rise in SNa. In a retrospective, single center series, Townsend et al.[32] found 6.4% of all LTx were supported with intra-operative CRRT. Of these, 37% had not been receiving RRT prior to LTx. In this series, 35% had supplemental $NaHCO_3$ added to replacement fluids. Unfortunately, no data were reported on peri-operative SNa changes. Overall, there is a paucity of data describing the practice of intra-operative CRRT during LTx.[33–36] Lenk et al.[37] report two cases of hyponatremic patients undergoing LTx with concomitant use of CRRT. Preparation of replacement and dialysate solutions with lower [Na] concentrations and infusion of hypotonic fluids assured a slow increase in sodium during the surgery (6–7 mmol/L), without neurological complications. In addition to a broader program of awareness to identify pre-operative hyponatremia in patients scheduled to receive LTx, along with educating about the potential iatrogenic complications of rapid SNa shift, our quality assurance review implemented a standardized assessment and protocol to management peri-operative hyponatremia among those receiving intra-operative CRRT to mitigate the risk of rapid SNa shift and ODS.

Limitations

While our study is one few to specifically focus on iatrogenic peri-operative SNa shift in hyponatremic patients undergoing LTx, we recognize it has notable limitations. First, our study is relatively small, with only six patients having a rapid increase in SNa identified. Second, our study is retrospective and represents the experience of single center. Accordingly, our study has limited statistical power, may be prone to type I error and may have limited generalizability with respect to other LTx centers. Third, we were unable to confirm whether patients had a clinical and/or radiographic diagnosis of ODS. Instead, we used a variety of neurologic outcomes as surrogates. However, we recognize the clinical findings of ODS may be heterogeneous in the post-operative LTx population and the diagnosis challenging. We contend, however, our data suggest rapid SNa shifts are not uncommon and that at-risk patients can be potentially identified pre-operatively. Finally, whereas ODS is often associated with severe hyponatremia, most of our patients had only moderate hyponatremia. We believe further prospective observational surveillance on this issue is warranted.

Conclusions

In summary, hyponatremia is present in a significant number of patients undergoing LTx, many of whom may be subjected to an iatrogenic rapid peri-operative rise in SNa. This rapid rise is associated with post-operative neurologic abnormalities that may result from pontine or extra-pontine myelinolysis. Fluid accumulation and intra-operative CRRT are risk factors for rapid rises in SNa. Following a quality assurance review, we were able to effectively identify and eliminate iatrogenic rapid shifts in SNa. Further efforts to identify at-risk patients and ensure SNa increases at a safe rate in the peri-operative period are needed, and clinical suspicion for ODS should remain high as its manifestations are variable.

Acknowledgements

Dr Bagshaw holds a Canada Research Chair in *Critical Care Nephrology* and is a Clinical Investigator supported by Alberta Innovates – Health Solutions (AI-HS).

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Strange K. Regulation of solute and water balance and cell volume in the central nervous system. *JASN.* 1992;3(1):12–27.
2. Lampl C, Yazdi K. Central pontine myelinolysis. *Eur Neurol.* 2002; 47(1):3–10.
3. Lien YH, Shapiro JI, Chan L. Study of brain electrolytes and organic osmolytes during correction of chronic hyponatremia. Implications for the pathogenesis of central pontine myelinolysis. *J Clin Invest.* 1991;88(1):303–309.
4. Sterns RH. Severe symptomatic hyponatremia: Treatment and outcome. A study of 64 cases. *Ann Intern Med.* 1987;107(5):656–664.
5. Sterns RH, Cappuccio JD, Silver SM, et al. Neurologic sequelae after treatment of severe hyponatremia: A multicenter perspective. *JASN.* 1994;4(8):1522–1530.
6. Soupart A, Penninckx R, Stenuit A, et al. Treatment of chronic hyponatremia in rats by intravenous saline: Comparison of rate versus magnitude of correction. *Kidney Int.* 1992;41(6):1662–1667.
7. Oh MS, Kim HJ, Carroll HJ. Recommendations for treatment of symptomatic hyponatremia. *Nephron.* 1995;70(2):143–150.
8. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: Expert panel recommendations. *Am J Med.* 2013;126(10 Suppl 1):S1–S42.
9. Yun BC, Kim WR, Benson JT, et al. Impact of pretransplant hyponatremia on outcome following liver transplantation. *Hepatology.* 2009;49(5):1610–1615.
10. Dawwas MF, Lewsey JD, Neuberger JM, et al. The impact of serum sodium concentration on mortality after liver transplantation: a cohort multicenter study. *Liver Transplant.* 2007;13(8):1115–1124.
11. Gines P, Berl T, Bernardi M, et al. Hyponatremia in cirrhosis: From pathogenesis to treatment. *Hepatology.* 1998;28(3):851–864.
12. Bichet D, Szatalowicz V, Chaimovitz C, et al. Role of vasopressin in abnormal water excretion in cirrhotic patients. *Ann Intern Med.* 1982;96(4):413–417.
13. Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology.* 1988; 8(5):1151–1157.
14. Senzolo M, Ferronato C, Burra P. Neurologic complications after solid organ transplantation. *Transplant Int.* 2009;22(3):269–278.
15. Hackworth WA, Heuman DM, Sanyal AJ, et al. Effect of hyponatraemia on outcomes following orthotopic liver transplantation. *Liver Int.* 2009;29(7):1071–1077.
16. Li C, Wen TF, Yan LN, et al. Risk factors for in-hospital mortality of patients with high model for end-stage liver disease scores following living donor liver transplantation. *Ann Hepatol* 2012; 11(4):471–477.
17. Karapanagiotou A, Kydona C, Papadopoulos S, et al. The effect of hyponatremia on the outcome of patients after orthotopic liver transplantation. *Transplant Proc.* 2012;44(9):2724–2726.
18. Lee J, Kim DK, Lee JW, et al. Rapid correction rate of hyponatremia as an independent risk factor for neurological complication following liver transplantation. *Tohoku J Exp Med.* 2013;229(2):97–105.
19. Yu J, Zheng SS, Liang TB, et al. Possible causes of central pontine myelinolysis after liver transplantation. *WJG.* 2004; 10(17):2540–2543.
20. Lee EM, Kang JK, Yun SC, et al. Risk factors for central pontine and extrapontine myelinolysis following orthotopic liver transplantation. *Eur Neurol.* 2009;62(6):362–368.

21. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology.* 2001; 33(2):464–470.
22. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373–383.
23. Londono MC, Guevara M, Rimola A, et al. Hyponatremia impairs early posttransplantation outcome in patients with cirrhosis undergoing liver transplantation. *Gastroenterology.* 2006; 130(4):1135–1143.
24. Estol CJ, Faris AA, Martinez AJ, et al. Central pontine myelinolysis after liver transplantation. *Neurology.* 1989;39(4):493–498.
25. Wszolek ZK, McComb RD, Pfeiffer RF, et al. Pontine and extrapontine myelinolysis following liver transplantation. Relationship to serum sodium. *Transplantation.* 1989; 48(6):1006–1012.
26. Abbasoglu O, Goldstein RM, Vodapally MS, et al. Liver transplantation in hyponatremic patients with emphasis on central pontine myelinolysis. *Clin Transplant.* 1998;12(3):263–269.
27. Park C, Kim D, Choi J, et al. Intraoperative changes in hyponatremia as a risk factor for prolonged mechanical ventilation after living donor liver transplantation. *Transplant Proc.* 2010; 42(9):3612–3616.
28. Boon AP, Carey MP, Adams DH, et al. Central pontine myelinolysis in liver transplantation. *J Clin Pathol.* 1991;44(11):909–914.
29. Singh N, Yu VL, Gayowski T. Central nervous system lesions in adult liver transplant recipients: Clinical review with implications for management. *Medicine.* 1994;73(2):110–118.
30. Zivkovic SA. Neurologic complications after liver transplantation. *World J Hepatol.* 2013;5(8):409–416.
31. Odier C, Nguyen DK, Panisset M. Central pontine and extrapontine myelinolysis: from epileptic and other manifestations to cognitive prognosis. *J Neurol.* 2010; 257(7):1176–1180.
32. Townsend DR, Bagshaw SM, Jacka MJ, et al. Intraoperative renal support during liver transplantation. *Liver Transpl.* 2009; 15(1):73–78.
33. Bellomo R, Harris C, Kang Y, et al. Combined veno-venous bypass and high volume hemofiltration during orthotopic liver transplantation. *ASAIO J.* 1993; 39(4):954–956.
34. Korbet SM, Casey C, Rodby RA, et al. The use of continuous arteriovenous hemofiltration in orthotopic liver transplantation. *Clin Nephrol.* 1995;43(2):134–136.
35. Salord F, Bailly MP, Gaussorgues P, et al. Continuous arteriovenous hemodialysis during emergency hepatic retransplantation: Two case reports. *Intensive Care Med.* 1990; 16(5):330–331.
36. Parmar A, Bigam D, Meeberg G, et al. An evaluation of intraoperative renal support during liver transplantation: a matched cohort study. *Blood Purif.* 2011;32(3):238–248.
37. Lenk MR, Kaspar M. Sodium-reduced continuous venovenous hemodiafiltration (CVVHDF) for the prevention of central pontine myelinolysis (CPM) in hyponatremic patients scheduled for orthotopic liver transplantation. *J Clin Anesth.* 2012; 24(5):407–411.