Moderate-to-Large Increases in Perioperative Serum Sodium Concentration Associated With Adverse Neurologic Events After Continuous Flow Left Ventricular Assist Device Implantation

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Objective: **It was hypothesized that preoperative hyponatremia is associated with increased 30-day mortality after left ventricular assist device placement, and that large increases in sodium concentration are associated with adverse neurologic events and 30-day mortality.**

Design: **Data were collected retrospectively on all patients having continuous flow left ventricular assist device implantation between January 1, 2009 and March 31, 2013. Preoperative variables, operative variables, and perioperative sodium concentrations were recorded. Both 30-day mortality and 72-hour adverse neurologic events (stroke or seizure) were recorded as primary outcome variables. Preoperative sodium and Δ sodium (postoperative sodium-preoperative sodium) were analyzed as tests for 30-day mortality and adverse neurologic events using receiver operating characteristic curves. Both crude and adjusted logistic regression analyses were used to estimate odds ratios for the outcome variables.**

Setting: **Tertiary care academic medical center.**

Participants: **Patients having durable continuous flow left ventricular assist device placement.**

Interventions: **None.**

Measurements and Main Results: **Among 88 patients, 30-day mortality was 14% (12 of 88) and the rate of perioperative stroke or seizure was 9% (8 of 88). There were 3 strokes and 5 tonic-clonic seizures. Preoperative sodium was a poor discriminative test for 30-day mortality and stroke or seizure (AUC = 0.47 and 0.57, respectively). Δ sodium was a poor discriminative test for 30-day mortality, but a fair discriminative test for stroke or seizure (AUC = 0.55 and 0.78, respectively). Δ sodium was a good discriminative test for seizure alone (AUC = 0.82) and a fair discriminative test for stroke alone (AUC = 0.70). It also increased the odds of stroke or seizure significantly, even when adjusting for possible confounders.**

Conclusions: **Moderate-to-large increases in sodium concentration during left ventricular assist device placement appear to be associated with adverse postoperative neurologic events. Preoperative hyponatremia has no relationship with 30-day mortality or adverse perioperative neurologic events.**

KEY WORDS: hyponatremia, stroke, seizure, ventricular assist device, mortality

MORE THAN 5 MILLION adults in the United States carry a diagnosis of heart failure.[1] Heart transplantation remains the only definitive therapy for this chronic condition despite advances in medical management. Unfortunately, the number of patients on the heart transplant waiting list far exceeds the number of donor hearts. Another therapeutic option for end-stage heart failure patients is mechanical circulatory support with durable, implantable devices that provide sufficient cardiac output to meet the patients' metabolic demands as both a bridge to transplantation or for destination therapy. Improving technology and insertion technique with increased management experience have helped left ventricular assist devices (LVADs) become an important option for these patients. In 2011, more than 1,600 LVADs were implanted in the United States.[2] The number of LVADs implanted is expected to rise with the increasing prevalence of heart failure, which is projected to increase by 25% by the year 2030,[1] and improving outcomes from destination therapy. For these reasons, a solid understanding of LVAD-related complications increasingly is necessary for healthcare providers.

Patients with LVADs are susceptible to adverse events, with up to 90% experiencing an event within 60 days of implantation.[3] Complications, including right ventricular failure, anemia, and coagulopathy, are common during the postoperative period.[4] Electrolyte disturbances in LVAD patients and their impact on outcomes previously have not been addressed in much detail. In hospitalized patients with cirrhosis, kidney disease, heart failure, and recent surgery, hyponatremia is common and predicts a worse outcome, including higher mortality.[5–10] Hyponatremia and fluctuations in serum sodium concentration also have been associated with increased intensive care unit (ICU) mortality.[11] Specifically, changes in serum sodium >12 mmol/L are associated with increased ICU mortality, with a proportional increase for greater fluctuation.[9] Similar relationships have been found in cardiac surgery patients, with preoperative, postoperative, and ICU-acquired sodium disturbances all being associated with higher mortality.[12–14]

To the authors' knowledge, there are no published studies of hyponatremia and outcomes in patients after LVAD implantation. The objective of this study was to examine the effect of preoperative hyponatremia and perioperative sodium changes on 30-day mortality and adverse postoperative neurologic events in patients undergoing durable LVAD implantation. It was hypothesized that preoperative hyponatremia would be associated with increased 30-day mortality and that large increases in serum sodium concentration during the perioperative period would be associated with 30-day mortality and adverse postoperative neurologic events.

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METHODS

Emory University's institutional review board approved the study, and a waiver of informed consent was granted to perform a retrospective data review. All continuous flow nonpulsatile left ventricular assist device implantations that were performed at the authors' center between January 1, 2009 and March 31, 2013 were identified via an electronic medical record query. Two surgeons performed all of the identified implantations. All patients had LVAD implantation performed using cardiopulmonary bypass with mild hypothermia and using consistent de-airing practices. Patients received an isoflurane- and fentanyl- based anesthetic. They also received tranexamic acid (TXA) with a loading dose of 15 mg/kg and a maintenance dose of 7.5 mg/kg/h during their operative course. Midazolam was administered for line placement before induction and not for anesthetic maintenance in the operating room.

For each individual patient, the following data were collected: Demographic data (age, gender, weight); surgical data (diagnosis, indication for surgery, Intermacs (The international registry for mechanically assisted circulatory support) class, device type, cardiopulmonary bypass time, total red cell transfusion, total platelet transfusion, total plasma transfusion); preoperative laboratory values (hematocrit concentration, platelet count, international normalized ratio, activated partial thromboplastin time, creatinine, estimated creatinine clearance, preoperative sodium); and preoperative comorbidities (poor mobility, peripheral vascular disease, cerebrovascular disease-previous stroke, previous cardiac surgery, chronic lung disease, endocarditis, intra-aortic balloon pump, inotrope use, diabetes mellitus, New York Heart Association class, right ventricular dysfunction, left ventricular ejection fraction, pulmonary hypertension, and atrial fibrillation). Δ sodium also was calculated for all patients, which was defined as the first postoperative serum sodium (all patients had this done by the end of the first postoperative day) minus the preoperative serum sodium measurement. All patients in the study received Plasmalyte 148 (Baxter International, Deerfield, IL) as their crystalloid fluid in the operating room and intensive care unit, because this is the standard fluid used at the authors' center. Some patients also received 5% albumin.

Definitions for most preoperative comorbidities were based on those currently listed on the EuroSCORE website. Creatinine clearance was estimated using the Cockcroft-Gault equation and the patient's preoperative creatinine. Extracardiac arteriopathy was defined as any of the following: Claudication, carotid occlusion or $>50\%$ stenosis, amputation, or previous/planned intervention on the abdominal aorta, limb arteries, or carotid arteries. Poor mobility was defined as severe impairment of mobility secondary to stroke or neuromuscular disease. Chronic lung disease was defined as long-term use of bronchodilators or steroids for lung disease or a history of obstructive sleep apnea. Pulmonary hypertension was defined as moderate (baseline pulmonary artery systolic pressure 31-55 mmHg) or severe (baseline pulmonary artery systolic pressure >55 mmHg). Right ventricular dysfunction was classified as mild, moderate, or severe based on the preoperative echocardiogram.

Finally, the following outcome measures were collected for all patients: Postoperative length of stay, 30-day mortality, postoperative tracheostomy, postoperative re-exploration for bleeding, 72-hour postoperative stroke or seizure (S/S), and postoperative acute renal failure. The primary outcome variables were 30-day mortality and S/S. Postoperative stroke was defined as any persistent new focal neurologic deficit or evidence of new stroke on imaging with an abnormal neurologic exam. Postoperative acute renal failure was defined according to the RIFLE criteria (RIFLE state F [Failure] with creatinine 3× baseline value, increase to greater than 4 mg/dL, or initiation of renal replacement therapies).

Statistical Analyses

All statistical analyses were performed using SPSS 21 (SPSS, Chicago, IL). Patient variables were examined for normality using histograms and the Shapiro-Wilk test. Normally distributed continuous variables were listed in tables as mean ± standard deviation, and non-normally distributed continuous variables were listed in tables as median [Q1, Q3]. Nominal variables were listed as number (%). The frequencies of the outcome variables were examined and noted to be small. Because stroke and seizure were uncommon events ($<10\%$ of individuals) and the cohort size also was relatively small, stroke and seizure events were grouped into a composite outcome variable called "S/S".

To preliminarily evaluate the relationships among preoperative sodium, Δ sodium, and the primary outcome variables, 30-day mortality and S/S, receiver operating characteristic (ROC) curves were created. The following ROC curves were analyzed: (1) preoperative sodium and 30-day mortality, (2) Δ sodium and 30-day mortality, (3) preoperative sodium and S/S, and (4) Δ sodium and S/S. Because the ROC curve for Δ sodium and S/S was found to have fair discriminative value and the others were not, separate ROC curves were created for Δ sodium and stroke and Δ sodium and seizure to determine whether one outcome was primarily responsible for driving the relationship with the composite outcome variable.

Bivariate logistic regression analyses were performed to estimate the crude relationships between preoperative sodium, Δ sodium, and the primary outcome variables (30-day mortality and S/S). Because the outcome variables were uncommon and the cohort was small, a maximum of two independent variables were included in any logistic regression model to limit the problem of model overfitting. For each outcome variable, important confounders were preselected to include an adjusted model if either preoperative sodium or Δ sodium was found to have a significant association with the outcome. In the 30-day model, the prespecified confounders were age, red cell transfusion, cardiopulmonary bypass time, glomerular filtration rate (GFR), and either preoperative sodium or Δ sodium. For the S/S model, the confounders were age, atrial fibrillation, cerebrovascular disease-previous stroke, diabetes mellitus, and either preoperative sodium or Δ sodium.

Binary logistic regression was performed using maximum likelihood estimation to estimate odds ratios [OR]. Wald statistics were used to test the null hypothesis that a given odds ratio was equal to 0. For adjusted models, the significance of the added confounder to the model was tested using likelihood ratios. The Nagelkerke r^2 was reported as a measure of model discrimination and the Hosmer-Lemeshow statistic was reported as a measure of model calibration. For preoperative sodium or Δ sodium in a particular model, odds ratios, 95% confidence intervals, and p values were reported.

RESULTS

A total of 88 patients underwent LVAD implantation at the authors' center during the study period. No patients were excluded from the analyses, and patient characteristics are listed in Table 1. Most LVAD insertions used the Heartmate II (Thoratec Corp., Pleasanton, CA) device, with only a small number of patients receiving the Heartware device (Heartware Inc., Framingham, MA). The most common diagnosis was nonischemic dilated cardiomyopathy. The indications for surgery were relatively evenly split between destination therapy and bridge to transplant. The median preoperative sodium for the cohort was 132 mmol/L, with a minimum value of 114 mmol/L and a maximum value of 141 mmol/L. The median Δ sodium for the cohort was 4 mmol/L, with a minimum value of –5 mmol/L and a maximum value of 14 mmol/L. Most patients had a positive Δ sodium (91.0%), and 8 patients (9.0%) had a negative Δ sodium.

Table 2 shows the incidence of relevant outcomes for the study. Overall 30-day mortality was 14% (12 of 88), and the overall rate of S/S was 9% (8 of 88). Three patients had