Vasopressin Deficiency and Vasodilatory State in End-Stage Liver Disease

Gebhard Wagener, MD,* Galina Kovalevskaya, PhD,† Moury Minhaz, BS,* Fallon Mattis, MD,* Jean C. Emond, MD,‡ and Donald W. Landry, MD, PhD§

Objectives: **Relative vasopressin deficiency, a contributor to vasodilatory septic shock, also may be a cause of the vasodilatory state in liver disease. This study assessed endogenous vasopressin levels in patients with liver disease and their hemodynamic response to exogenous vasopressin.**

Design: **A prospective, observational study.**

Setting: **A single-center, tertiary hospital.**

Participants: **Human subjects undergoing liver transplantation or major surgery.**

Interventions: **Vasopressin levels were measured in 28 patients with liver disease undergoing liver transplantation and 7 control patients with normal liver function. Additionally, intravenous vasopressin was administered to 20 liver transplant recipients, and the hemodynamic response was observed.**

Measurements and Main Results: **Patients with liver disease had significantly lower baseline vasopressin levels than controls (19.3 ± 27.1 pg/mL *v* 50.9 ± 36.7 pg/mL, $p = 0.015$). Patients with low vasopressin levels (≤20 pg/mL) were more likely to have lower baseline mean blood pressure (≤80 mmHg) than patients with high vasopressin levels (11/16 *v* 0/4, $p = 0.013$). Systemic vascular resistance increased by 33% 3 minutes after intravenous vasopressin. Thirteen of 16 patients with low vasopressin levels compared with 1 of 4 patients with high vasopressin levels responded to exogenous vasopressin, with an increase of mean blood pressure by more than 20% ($p = 0.028$).**

Conclusions: **Patients with liver disease have lower vasopressin levels than controls and respond with a brisk vasoconstrictor response to exogenous vasopressin. Therefore, relative endogenous vasopressin deficiency may contribute to vasodilatory shock in liver disease similar to what has been observed in septic shock.**

KEY WORDS: hepatic cirrhosis, vasopressor, liver transplantation, vasopressin deficiency, vasoconstrictors, vasodilation

END-STAGE LIVER DISEASE causes arterial vasodilation despite high levels of endogenous catecholamines and angiotensin, resulting in maldistribution of blood flow and low perfusion pressure.[1-4] This hemodynamic condition is similar to what previously has been observed during prolonged septic shock. Vasodilation in septic shock is exacerbated by relative vasopressin deficiency; endogenous levels of vasopressin are low in septic shock,[5] and a low-dose infusion of exogenous vasopressin that would otherwise have no effect on blood pressure in healthy subjects can restore pressure tone in these patients.[6] In liver failure, vasopressin analogs (terlipressin or ornipressin) are able to reverse hepatorenal syndrome and restore renal function,[7,8] similar to the effect of vasopressin in septic shock.[9] Methylene blue also has been suggested as a treatment for vasopressor-resistant vasoplegia syndrome in liver transplantation[10] but probably should be reserved only for situations in which other vasopressors failed to maintain adequate perfusion pressure.

This study aimed to evaluate the role of endogenous vasopressin in the vasodilatory state in liver disease. The hypothesis that patients with end-stage liver disease have lower baseline vasopressin levels when compared with patients with normal liver function was tested. The authors further hypothesized that patients with end-stage liver disease are more likely to be relatively vasopressin deficient, defined as low-to-normal baseline vasopressin levels (under 20 pg/mL) combined with low baseline blood pressure (mean arterial blood pressure <80 mmHg) and a pronounced sensitivity to exogenous vasopressin (an increase of mean arterial blood pressure by more than 20% as a response to an intravenous bolus of 3 U of arginine vasopressin) compared with patients with normal liver function.

METHODS

The Institutional Review Board of Columbia University approved this study. The authors obtained informed signed consent from all patients who participated in this study. All adult patients undergoing liver transplantation (cadaveric or living related) at Columbia-University Medical Center were eligible for inclusion. Adult patients undergoing a Whipple operation or partial hepatectomies were included as controls because these patients also underwent major surgery comparable to liver transplantation but had normal preoperative liver function. Patients with liver disease, abnormal liver function tests, or abnormal coagulation tests were excluded from the control group.

In all liver transplant patients, a pulmonary artery catheter (with continuous cardiac output and mixed venous oxygen saturation measurement; Edwards Lifesciences, Irvine, CA) was inserted per routine before surgery. Additionally, an 18F gastric tonometry tube (Datex-Ohmeda, Madison, WI) was inserted into the stomach to measure gastric mucosal carbon dioxide partial pressure (pCO_2). None of the control patients received a pulmonary artery catheter or a gastric tonometry tube.

Anesthesia for all patients (liver transplants and controls) was induced with propofol or etomidate and succinylcholine and maintained with fentanyl and sevoflurane. Muscle relaxation was achieved by using cisatracurium. There was no significant difference in the groups (responders and nonresponders) with regard to the anesthetic technique

*From the Departments of *Anesthesiology, ‡Surgery, and §Medicine, and †Irving Institute for Clinical and Translational Research, College of Physicians and Surgeons, Columbia University, New York, NY.*

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Address reprint requests to Gebhard Wagener, MD, Department of Anesthesiology, Columbia University, P&S Box 46 (PH-5), 630 West 168th Street, New York, NY 10032-3784. E-mail: gw72@columbia.edu

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Table 1. Patient Characteristics

	OLT (n = 28)	Control (n = 7)	*p* Value
Preoperative			
Female, n (%)	10 (35.7)	5 (71.4)	NS
Age, mean ± SD, y	52.9 ± 12.5	52.0 ± 8.0	NS
MELD, mean ± SD	17.8 ± 9.0	8.7 ± 3.3	<0.05
BMI, mean ± SD	27.1 ± 5.8	25.9 ± 4.9	NS
Creatinine, mean ± SD (mg/dL)	1.19 ± 1.19	0.87 ± 0.45	NS
Total bilirubin, mean ± SD (mg/dL)	6.6 ± 9.3	0.9 ± 0.8	<0.005
INR	3.9 ± 11.9	1.04 ± 0.14	NS
Albumin	3.94 ± 5.15	4.14 ± 0.49	NS
Ascites, n (%)	13 (46.4)	0	NS
LRLT, n (%)	6 (21.4)	—	NS
Indication for surgery			
Hepatitis C, n (%)	16 (57.1)	0	
ETOH, n (%)	3 (10.7)	0	
PSC, n (%)	4 (14.3)	0	
HCC, n (%)	9 (32.1)	1 (14.3)	
Others, n (%)	5 (17.9)	2 (28.6)	
Pancreatic Ca, n (%)	—	3 (42.9)	
Living liver donor, n (%)	—	1 (14.3)	
Intraoperative			
Length of anesthesia, mean ± SD (h)	11.2 ± 2.5	9.2 ± 3.4	NS
Reoperation, n (%)	2 (7.1)	0	NS
PRBC, mean ± SD (U)	14.1 ± 4.8	4.4 ± 5.6	NS
FFP, mean ± SD (U)	15.4 ± 14.7	2.9 ± 4.2	<0.05

Abbreviations: BMI, body mass index; INR, international normalized ratio; LRLT, living related liver transplant; ETOH, alcohol-induced hepatic cirrhosis; PSC, primary sclerosing cholangitis; HCC, hepatocellular carcinoma; PRBC, number of packed red blood cells used intraoperatively; FFP, amount of fresh frozen plasma used intraoperatively; NS, not significant.

or the amount of anesthetic drugs or gases given to the patient by the time the vasopressin bolus and infusion were started.

In 20 patients undergoing liver transplantation, an intravenous bolus of 3 U of vasopressin (8-arginine-vasopressin; Monarch Pharmaceuticals Inc, Bristol, TN) was administered followed by a continuous intravenous infusion of 3 U/h for 20 minutes at the end of the dissection phase. It is the authors' clinical practice at Columbia University Medical Center to start a vasopressor infusion at this time point in order to prepare the patient for the anhepatic phase and caval cross-clamping. Eight patients undergoing liver transplantation did not receive vasopressin because they required vaoconstrictors for hypotension before the measurements (3 patients received vasopressin together with norepinephrine) or for logistic reasons (5 patients [the investigators were not available before the anhepatic phase of the liver transplant]). None of the control patients received vasopressin.

Three milliliters of arterial blood were drawn after the induction of anesthesia before surgery. The blood was spun immediately at 2,000*g* for 20 minutes at 4°C, and the plasma was frozen at −80°C. Vasopressin levels were determined using a commercially available radioimmune assay kit (Alpco, Salem, NH) according to the manufacturer's instructions. The intra-assay precision of this test was 6.0%, the inter-assay precision was 9.9% with an analytic sensitivity of 0.75 pg/mL, and the specificity was 1.3 pg/mL. The upper level of detection (undiluted) was 80 pg/mL.[11] Any level above 80 pg/mL was defined as 80 pg/mL for the purpose of statistical calculations.

Values are presented as mean ± standard deviation. Comparisons of paired variables were made either using a paired *t* test for variables with normal distribution or Wilcoxon matched pairs test for variables without Gaussian distribution. Gaussian distribution was determined using the Kolmogorov-Smirnov test. The Pearson correlation was used when evaluating the correlation of 2 continuous variables. To evaluate the hemodynamic response to vasopressin, a repeated measures 1-way analysis of variance (ANOVA) and a post hoc test for linear trend were used; p values were 2 tailed, and $p < 0.05$ was considered significant.

The authors based the sample size analysis on their first hypotheses that patients with end-stage liver disease had lower baseline vasopressin levels when compared with patients with normal liver function. For the purpose of estimating the sample size, the authors assumed that patients with end-stage liver disease had a baseline vasopressin level of 10 pg/mL and patients with normal liver function had a baseline vasopressin level of 20 pg/mL with a common standard deviation of 5 pg/mL. Setting an alpha level at 0.05, 4 patients would be required in each group to achieve a power ($1 - \beta$) of 0.8. Seven controls were enrolled to compensate for potential problems with the measurements and 20 subjects to adequately address hypothesis 2. SPSS 17.0 (SPSS Inc, Chicago, IL) and Graphpad Prism 4.0 (San Diego, CA) software were used for the statistical analysis.

RESULTS

After obtaining informed, signed consent, 28 patients undergoing liver transplantations and 7 control patients (2 Whipple operations and 5 partial hepatectomies) were enrolled. The demographic information is listed in Table 1.

Eight patients had vasopressin levels above the level of detection of 80 pg/mL (4/28 liver transplant recipients [14.3%] and 4/7 controls [57.1 %], $p = 0.01$). Patients receiving liver transplants had significantly lower vasopressin levels than control patients (19.3 ± 27.1 pg/mL *v* 50.9 ± 36.7 pg/mL, $p = 0.015$; Fig 1).

Eight liver transplant patients did not receive vasopressin as per protocol because they either required a vasopressor (norepinephrine and vasopressin infusion) before initiation of the

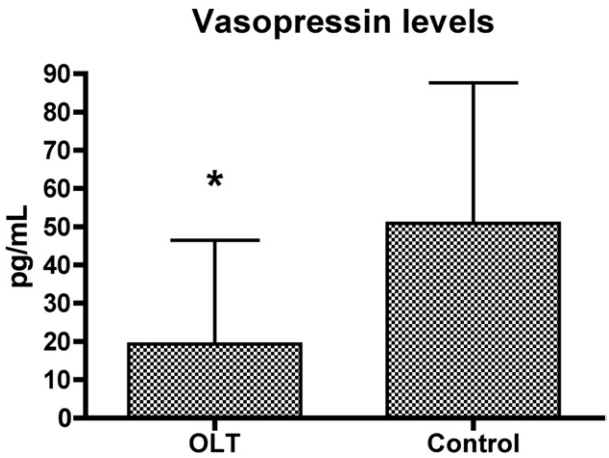

Fig 1. Baseline vasopressin levels in patients with liver disease undergoing liver transplantations (OLT, n = 28) and control patients with normal liver function undergoing hepatectomies or Whipple procedures (n = 7; mean ± SD, *$p < 0.05$). Four OLT and 4 control patients had baseline vasopressin levels above the detection limit of 80 pg/mL, and their levels were defined as 80 pg/mL.