

Severe hemodynamic instability in a patient with suspected hepatoadrenal syndrome during liver transplantation -A case report-

Seong-Soo Choi, Jihion Yu, Young-Kug Kim, and Gyu-Sam Hwang

Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Adrenal insufficiency, which is related to hemodynamic instability and increased mortality, has been reported in patients with advanced liver disease regardless of the presence of septic conditions. In this regard, the hepatoadrenal syndrome has been recently proposed as adrenal insufficiency in critically ill patients with liver disease. We describe here a 67-year-old female patient with hepatic failure and adrenal insufficiency. The patient showed stable vital signs and no evidence of sepsis preoperatively. Despite hydrocortisone replacement and inotropics administration, severe intraoperative hemodynamic instability was observed. Hydrocortisone administration was continued postoperatively, nevertheless inotropics could not be tapered. On postoperative day 11, the patient died due to pneumonia and septic shock. Hepatoadrenal syndrome may have played a key role in her severe hemodynamic fluctuation and poor outcome, reinforcing the importance of adrenal function in the liver transplantation surgery. (Korean J Anesthesiol 2013; 64: 536-540)

Key Words: Adrenal insufficiency, Hepatic failure, Hepatoadrenal syndrome, Liver transplantation.

Adrenal insufficiency is related to catecholamine-resistant hemodynamic instability and is associated with high mortality rates in critically ill patients [1,2]. Adrenal insufficiency has been observed in patients with advanced liver disease, with or without septic conditions [3,4]. Moreover, 62% of critically ill patients with liver failure have shown subclinical adrenal insufficiency [5], and 92% of patients undergoing liver transplantation with steroid-free immunosuppression have been diagnosed with adrenal insufficiency [3]. It has been revealed

that both sepsis and end-stage liver disease have a number of common pathophysiologic mechanisms, such as endotoxemia, increased levels of pro-inflammatory mediators, and decreased apoprotein-A/high-density lipoprotein levels [3,5-7]. Recently, a new disease concept, "hepatoadrenal syndrome", has been proposed specifically according to the finding of the adrenal insufficiency in critically ill patients with liver disease [3], although whether adrenal insufficiency in liver disease is specific to liver failure is not known exactly [8].

Received: July 4, 2012. Revised: August 9, 2012. Accepted: August 10, 2012.

Corresponding author: Young-Kug Kim, M.D., Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, 388-1, Pungnap-2dong, Seoul 138-736, Korea. Tel: 82-2-3010-3868, Fax: 82-2-470-1363, E-mail: kyk@amc.seoul.kr

©This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

We describe here a patient with suspected hepatoadrenal syndrome who was diagnosed preoperatively with adrenal insufficiency in the absence of overt sepsis and subsequently developed severe hemodynamic instability during and after living donor liver transplantation.

Case Report

A 67-year-old female patient with adrenal insufficiency in drug-induced hepatic failure previously had a cancer on the left breast, which had been treated by modified radical mastectomy followed by an unknown regimen of adjuvant chemotherapy. Thereafter, she had experienced jaundice with mental change and had been diagnosed with drug-induced liver failure. Despite supportive care, her stuporous mental status did not return, making her a candidate for liver transplantation. Although she was semicomatose, her vital signs were stable and there was no evidence of sepsis. Laboratory analysis revealed unexplained hyponatremia of 121–124 mmol/L and K⁺ concentration of 4.8–5.4 mmol/L (Table 1). A rapid adrenocorticotropic hormone (ACTH) stimulation test was performed to diagnose adrenal insufficiency. Her preoperative random total cortisol concentration was 9.0 µg/dl (adrenal insufficiency: < 10 µg/dl). Thirty minutes after stimulation with 250 µg synacthen, her delta cortisol concentration was 4.9 µg/dl (adrenal insufficiency: < 9 µg/dl). The concentrations of all the other hormones were within the normal ranges. Based on guidelines for the diagnosis of corticosteroid insufficiency in critically ill patients [9], she was diagnosed with adrenal insufficiency. The patient was started on hydrocortisone therapy (50 mg, tid) preoperatively, and it was maintained during liver transplantation.

Anesthesia was induced with thiopental sodium, fentanyl,

vecuronium, and sevoflurane. Hemodynamic data were recorded in real time during surgery using an online personal computer interfaced with a signal processing software (Windaq, DATAQ instrument, Akron, OH). Thirty minutes after surgical incision, the patient’s mean arterial blood pressure (ABP) started to fluctuate and decreased to less than 60 mmHg without significant blood loss. Because intermittent bolus administration of ephedrine was not effective, she was infused continuously with dopamine (5–10 µg/kg/min), dobutamine (5 µg/kg/min) and norepinephrine (0.15–0.2 µg/kg/min), starting from the pre-anhepatic phase of liver transplantation (Table 1). However, her ABP fluctuated markedly (Fig. 1). Before graft reperfusion, she was administered 172.5 mg of methylprednisolone (3 mg/kg) for immunosuppression. Immediately after reperfusion, she was administered 40 µg of an epinephrine bolus due to severe hypotension. However, although she was supported by increasing dose of inotropics and vasopressors after graft reperfusion, her ABP continued to fluctuate until the end of the operation. Blood components transfused during operation were shown in Table 2.

Although she was maintained on hydrocortisone postoperatively, inotropics could not be tapered and hemodynamic instability continued (Table 1). On postoperative day 9, the patient developed atrial fibrillation, and a chest radiograph showed pneumonic infiltration. On postoperative day 11, the patient died due to pneumonia and septic shock.

Discussion

Adrenal insufficiency is relatively common in critically ill patients [9,10]. Interestingly, there is a high incidence of adrenal insufficiency in critically ill patients with liver disease [3]. Harry

Table 1. Hemodynamic Variables, Cortisol Level and Doses of Infused Inotropics during the Perioperative Period in a Liver Transplant Recipient with Suspected Hepatoadrenal Syndrome

	W	P	A	N-R	N-HA	N-BD	POD 1	POD 7	POD 9	POD 11
ABP (S/D/M) (mmHg)	111/53/73	108/42/67	99/45/63	102/49/67	92/46/61	108/51/70	126/50/75	101/61/73	95/64/74	58/53/54
HR (bpm)	72	78	85	93	79	83	93	103	76	62
CVP (mmHg)	-	10	9	13	12	9	7	10	11	5
PAP (S/D/M) (mmHg)	-	20/11/14	18/11/14	24/10/16	25/12/18	24/10/16	-	-	-	-
CO (L/min)	-	3.60	5.10	5.10	4.40	4.60	-	-	-	-
SVR (dynes-s/cm ⁵)	-	1142	617	759	1011	895	-	-	-	-
Cortisol (µg/dl)	9	-	-	-	-	-	244	21	-	-
Inotropics (µg/kg/min)										
Dopamine	-	5	10	-	-	-	-	-	15	20
Norepinephrine	-	0.15	0.15	0.15	0.18	0.20	0.30	0.12	0.40	0.40
Dobutamine	-	5	5	5	5	5	5	5	-	-
Epinephrine	-	-	-	-	-	-	-	-	0.10	0.10

W: ward, P: pre-anhepatic phase after induction of anesthesia, A: anhepatic phase, N-R: neohepatic phase 10 min after graft reperfusion, N-HA: neohepatic phase after hepatic artery anastomosis, N-BD: neohepatic phase after biliary duct reconstruction, POD: postoperative day, ABP: arterial blood pressure, S: systolic, D: diastolic, M: mean, HR: heart rate, CVP: central venous pressure, PAP: pulmonary arterial pressure, CO: cardiac output, SVR: systemic vascular resistance.

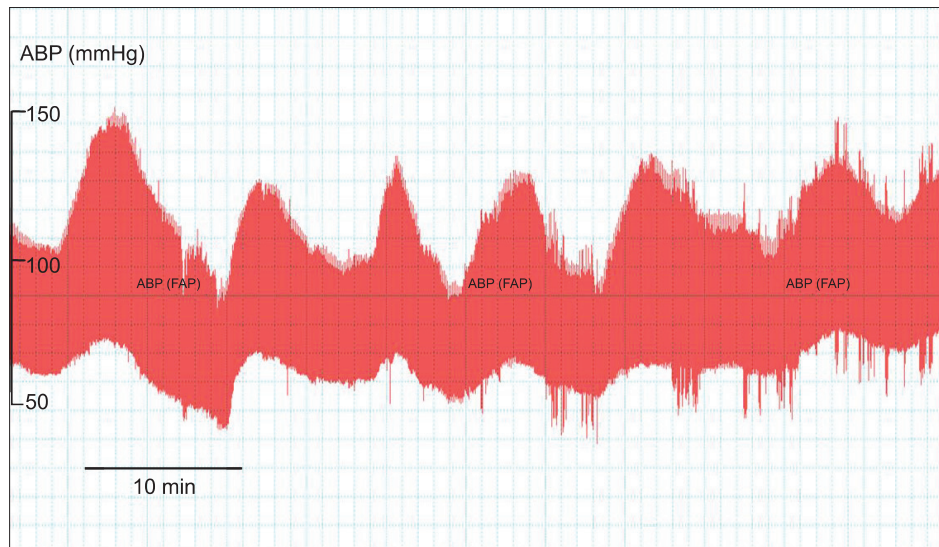


Fig. 1. Changes in arterial blood pressure (ABP) during the pre-anhepatic period of liver transplantation in a patient with suspected hepatoadrenal syndrome. Note that ABP fluctuated markedly 30 min after surgical incision, although blood loss was minimal. FAP: femoral arterial pressure.

Table 2. Arterial Blood Gas Analysis and Electrolytes Concentrations during the Perioperative Period, and Infused Blood Components during Operation in a Liver Transplant Recipient with Suspected Hepatoadrenal Syndrome

	W	P	A	N-R	N-HA	N-BD	POD 1	POD 7	POD 9	POD 11
Arterial pH	7.36	7.36	7.27	7.31	7.35	7.40	7.50	7.41	7.49	7.19
PaCO ₂ (mmHg)	36	36	26	28	29	33	26	44	36	20
FiO ₂	Room air	0.5	0.5	0.5	0.5	0.5	0.5	0.3	0.7	1.0
PaO ₂ (mmHg)	74	264	284	286	262	290	197	51	93	223
Bicarbonate (mEq/L)	21	20	12	14	16	20	21	28	27	8
Base excess (mEq/L)	-5.10	-4.70	-13.60	-11.10	-8.60	-3.90	-2.40	2.90	3.80	-20.60
Lactate (mmol/L)	0.80	1.80	3.00	3.10	2.50	1.80	1.70	1.20	3.00	17.60
Electrolytes										
Na ⁺ (mmol/L)	128	126	127	124	124	125	131	133	133	130
K ⁺ (mmol/L)	5.40	5.40	4.50	4.00	4.00	3.80	4.30	4.00	3.10	5.10
Ca ²⁺ (mmol/L)	1.78	1.69	1.80	1.53	1.04	1.17	1.18	1.33	1.17	1.15
Mg ²⁺ (mg/dl)	2.13	1.92	1.93	1.80	1.52	-	1.82	1.90	1.98	1.97
Blood components transfused during operation (units)										
RBCs	-	39	13	-	5	14	-	-	-	-
FFPs	-	49	16	-	4	9	-	-	-	-
PCs	-	8	-	-	8	8	-	-	-	-
Cryoprecipitates	-	10	-	-	10	-	-	-	-	-

W: ward, P: pre-anhepatic phase after induction of anesthesia, A: anhepatic phase, N-R: neohepatic phase 10 min after graft reperfusion, N-HA: neohepatic phase after hepatic artery anastomosis, N-BD: neohepatic phase after biliary duct reconstruction, POD: postoperative day, PaCO₂: arterial carbon dioxide partial pressure, FiO₂: inspired fraction of oxygen, PaO₂: arterial oxygen partial pressure, RBC: red blood cell, FFP: fresh frozen plasma, PC: platelet concentrate.

et al. [5] reported that hemodynamically unstable patients with acute hepatic dysfunction showed significantly lower serum cortisol levels of ACTH stimulation test. They also revealed that the steroid replacement was associated with dose reduction of vasopressor, but not survival, in patients with adrenal insufficiency in liver failure [4]. Furthermore, Marik et al. [3,7] have observed a pathophysiologic association between adrenal insufficiency and low concentrations of high-density lipoprotein, the preferred source of steroidogenic substrates in the adrenal gland, in patients with liver failure and in post-liver transplant

recipients. These findings have led to recognition of the disease entity “hepatoadrenal syndrome”. Our patient was not septic and she showed relatively stable vital signs preoperatively. Although hydrocortisone replacement started immediately after diagnosis of adrenal insufficiency, her hemodynamic status was unstable and she required continuous infusion of inotropics during and after liver transplantation. Therefore, she likely had hepatoadrenal syndrome, with adrenal insufficiency playing a role in her cardiovascular instability during and after liver transplantation.

Because most of liver transplant recipients receive supplementary corticosteroids as postoperative immunosuppressants, adrenal insufficiency has been rarely documented in those patients. After the development of steroid-free immunosuppression, several reports have shown adrenal insufficiency in post-liver transplant recipients [3,7,8,11]. For example, adrenal insufficiency, as manifested by severe multiple organ dysfunction, was observed in a post-liver transplant recipient who had not been administered with steroid immunosuppressants [11]. That patient had been diagnosed with adrenal insufficiency 40 days after liver transplantation and was successfully treated with corticosteroid [11]. However, there is little report focused on adrenal insufficiency that occurred before liver transplantation. Our report is a case of a liver transplant recipient to be diagnosed preoperatively with adrenal insufficiency, showing marked ABP fluctuation during liver transplantation surgery. It is well known that the basic concept of adrenal insufficiency is the inadequate activation of hypothalamic-pituitary-adrenal axis with cortisol release to illness and stress [3,7,9]. Even though the present patient showed relatively stable hemodynamic parameters before glucocorticoid replacement, she was treated with hydrocortisone throughout the hospital course after confirming adrenal insufficiency. However, surgical stress may not be tolerated and cause severe hemodynamic instability during liver transplantation despite hydrocortisone replacement therapy, implying importance of adrenal function in liver transplantation.

Several previous studies on patients with liver failure and adrenal insufficiency have focused on sepsis or septic conditions and survival by corticosteroid administration [4,5,12,13]. Previous studies have reported that corticosteroid therapy has beneficial effects on survival and hemodynamic stability in patients with liver failure and septic shock [5,13,14] and in post-liver transplant recipients [3,11-13]. However, consistent with findings showing that corticosteroid therapy may not improve survival in vasopressor-dependent patients with adrenal insufficiency and liver disease [4], our patient with suspected hepatoadrenal syndrome did not effectively respond to corticosteroid therapy, eventually expired due to pneumonia and septic shock after liver transplantation. The specific mechanisms underlying these controversial effects of steroid therapy are unknown, but warrant further investigation.

It has been well known that hemodynamic complications in patients with liver failure may be affected by several factors. For examples, low systemic vascular resistance, high cardiac output, combined cirrhotic cardiomyopathy, massive bleeding and coagulopathy, and metabolic status during liver transplantation may be involved in hemodynamic instability in liver failure patients [15]. Hemodynamic instability in the present patient during and after liver transplantation was not

explained completely by the general pathophysiology of liver failure. Because arterial pH, electrolytes, lactate level, and intravascular volume status during liver transplantation surgery were maintained adequately, adrenal insufficiency diagnosed preoperatively was thought to be an important reason for the marked ABP fluctuation during and after liver transplantation surgery in our patient. However, we could not exclude the above mentioned pathophysiological effects.

In conclusion, we found that a patient with adrenal insufficiency suffered severe hemodynamic instability during and after liver transplantation, reinforcing the importance of hepatoadrenal syndrome. These findings indicate that perioperative adrenal function should be monitored carefully in liver transplantation recipients with severe hemodynamic fluctuation.

References

1. Hoen S, Mazoit JX, Asehounne K, Brailly-Tabard S, Benhamou D, Moine P, et al. Hydrocortisone increases the sensitivity to alpha1-adrenoceptor stimulation in humans following hemorrhagic shock. *Crit Care Med* 2005; 33: 2737-43.
2. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *BMJ* 2004; 329: 480-4.
3. Marik PE, Gayowski T, Starzl TE. The hepatoadrenal syndrome: a common yet unrecognized clinical condition. *Crit Care Med* 2005; 33: 1254-9.
4. Harry R, Auzinger G, Wendon J. The effects of supraphysiological doses of corticosteroids in hypotensive liver failure. *Liver Int* 2003; 23: 71-7.
5. Harry R, Auzinger G, Wendon J. The clinical importance of adrenal insufficiency in acute hepatic dysfunction. *Hepatology* 2002; 36: 395-402.
6. Molenaar N, Bijkerk RM, Beishuizen A, Hempen CM, de Jong ME, Vermes I, et al. Steroidogenesis in the adrenal dysfunction of critical illness: impact of etomidate. *Crit Care* 2012; 16: R121.
7. Marik PE. Adrenal-exhaustion syndrome in patients with liver disease. *Intensive Care Med* 2006; 32: 275-80.
8. O'Beirne J, Holmes M, Agarwal B, Bouloux P, Shaw S, Patch D, et al. Adrenal insufficiency in liver disease - what is the evidence? *J Hepatol* 2007; 47: 418-23.
9. Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med* 2008; 36: 1937-49.
10. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 2003; 348: 727-34.
11. Iwasaki T, Tominaga M, Fukumoto T, Kusunoki N, Sugimoto T, Kido M, et al. Relative adrenal insufficiency manifested with multiple organ dysfunction in a liver transplant patient. *Liver Transpl* 2006; 12: 1896-9.
12. Tsai MH, Peng YS, Chen YC, Liu NJ, Ho YP, Fang JT, et al. Adrenal

- insufficiency in patients with cirrhosis, severe sepsis and septic shock. *Hepatology* 2006; 43: 673-81.
13. Fernandez J, Escorsell A, Zabalza M, Felipe V, Navasa M, Mas A, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: Effect of treatment with hydrocortisone on survival. *Hepatology* 2006; 44: 1288-95.
 14. Canabal JM, Kramer DJ. Management of sepsis in patients with liver failure. *Curr Opin Crit Care* 2008; 14: 189-97.
 15. Henriksen JH, Moller S. Cardiac and systemic haemodynamic complications of liver cirrhosis. *Scand Cardiovasc J* 2009; 43: 218-25.