

# Skin Necrosis after a Low-Dose Vasopressin Infusion through a Central Venous Catheter for Treating Septic Shock

Eun Hee Kim, M.D., Sae Hwan Lee, M.D., Seung Woon Byun, M.D.,  
Ho Suk Kang, M.D. Dong Hoe Koo, M.D.,  
Hyun-Gu Park, M.D. and Sang Bum Hong, M.D.

*Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Asan Medical Center,  
University of Ulsan College of Medicine, Seoul, Korea*

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This is a report on a case of severe skin necrosis in a vasodilatory septic shock patient after the infusion of low-dose vasopressin through a central venous catheter. An 84-year-old male was hospitalized for edema on both legs at Asan Medical Center, Seoul, Korea. On hospital day 8, the patient began to complain of dyspnea and he subsequently developed severe septic shock caused by *E. coli*. After being transferred to the medical intensive care unit, his hypotension, which was refractory to norepinephrine, was controlled by an infusion of low-dose vasopressin (0.02 unit/min) through a central venous catheter into the right subclavian vein. After the infusion of low-dose vasopressin, severe skin necrosis with bullous changes developed, necessitating discontinuation of the low-dose vasopressin infusion. The patient expired from refractory septic shock. Although low-dose vasopressin can control hypotension in septic shock patients, low-dose vasopressin must be used with caution because ischemic complications such as skin necrosis can develop even with administration through a central venous catheter.

**Key Words :** Arginine vasopressin, Septic shock, Necrosis

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## INTRODUCTION

Vasopressin is a potent vasopressor that improves organ perfusion during septic shock. Because vasopressin causes arterial smooth muscle cell contraction via the non-catecholamine receptor pathway, it represents an attractive adjunct for the management of septic shock, especially when catecholamines prove to be ineffective<sup>1)</sup>. Growing evidence has suggested that low-dose vasopressin (0.04 unit/min) is safe and effective for the treatment of vasodilatory septic shock. In a recent prospective randomized controlled study, a combined infusion of vasopressin and norepinephrine proved more effective than norepinephrine alone for the management of catecholamine-resistant vasodilatory shock<sup>2)</sup>. Vasopressin is recommended as a second-line agent for refractory septic

shock<sup>3)</sup>.

Peripheral administration is often preferred for the treatment of gastrointestinal bleeding such as esophageal varices because of the potential risk of myocardial ischemia that is related to central venous administration of higher doses of vasopressin (0.2~0.5 units/min)<sup>4-6)</sup>. Yet in some settings, peripheral administration of high-dose vasopressin has been reported to cause skin necrosis and gangrene if the drug infiltrates into soft tissue<sup>7-9)</sup>. In addition, peripheral administration of low-dose vasopressin has been reported to cause skin necrosis<sup>10, 11)</sup>. However, to the best of our knowledge, skin necrosis has never been reported in connection with low-dose vasopressin administered through a central venous catheter for the treatment of septic shock. Here we report on a patient with septic shock, who developed severe skin necrosis after infusion of low-dose

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• Correspondence to : Sang-Bum Hong, M.D., Department of Internal Medicine, Asan Medical Center, University of Ulsan, College of Medicine, #388-1 Pungnap-2 dong, Songpa-Gu, Seoul 138-600, Korea Tel : 82-2-3010-3893, Fax : 82-2-3010-6968, Email : sbhong@amc.seoul.kr



**Figure 1.** Skin necrosis in a vasodilatory septic shock patient treated with low-dose vasopressin. After the infusion, necrosis with variable sized bullous changes developed at both wrists and on both lower legs. In time, the skin lesions expanded to the both arms, both thighs and the abdomen.

vasopressin via a central venous catheter.

## CASE REPORT

An 84-year-old male was admitted to our hospital for edema on both legs that had developed 1 month earlier. Diabetes mellitus had been diagnosed 15 years earlier, and the patient had been controlling his blood sugar levels with insulin. Hypertension had been diagnosed one year earlier, hypertension, and the patient was regularly taking an angiotensin converting enzyme inhibitor and a calcium channel blocker. In addition, 7 years earlier, due to the right hand tremor, idiopathic Parkinsons disease had been diagnosed in this patient due to right hand tremor.

On the day of admission, the abdominal ultrasound examination showed alcoholic liver cirrhosis and small ascites around the liver. The serum albumin concentration was 2.5 g/dL, the serum bilirubin concentration was 2.4 mg/dL and the prothrombin time was 88%; this corresponded to Childs classification B. He had thrombocytopenia (platelets 79,000/mm<sup>3</sup>) and diabetic chronic renal failure (creatinine 2.2 mg/dL). The chest radiograph revealed mild cardiomegaly, and the brain natriuretic peptide was 193 pg/mL. The echocardiography showed that the left ventricle ejection fraction was 55%, which was within the normal range.

On hospital day 2, the leg edema was diagnosed as being caused by uncompensated liver cirrhosis combined with diabetic chronic renal failure. After administration of diuretics and albumin, the leg edema improved. However, he complained of a sudden onset of dyspnea on hospital day 8. By that time, he had developed tachycardia (123 beats/min), tachypnea (30

breaths/min) and hypoxemia (SaO<sub>2</sub> 80%). The creatine kinase, CK-MB and troponin-I levels were within the normal range. The electrocardiography showed no significant ST depression or elevation, essentially ruling out the possibility of acute myocardial infarction. The lung perfusion scan also eliminated the possibility of pulmonary embolism. Despite oxygen supplementation (a mask with reservoir bag 10 L/min), the patient failed to maintain a SaO<sub>2</sub> above 90%, and his severe tachypnea (32 breaths/min) was also exacerbated. After the preliminary diagnosis of septic shock and endotracheal intubation, the patient was transferred to the intensive care unit.

On the first day in the intensive care unit, his vital signs were indicative of hypotension (the blood pressure 75/40 mm Hg; the mean arterial pressure 48 mm Hg), exacerbated tachycardia (130 beats/min) and hypothermia (34°C). The laboratory examination results showed that the WBC was 700/mm<sup>3</sup>, the Hb was 9.7 g/dL, the platelet count was 59,000/mm<sup>3</sup>, the BUN/Cr was 57/2.2 mg/dL, C-reactive protein was 8.3 mg/dL and the lactic acid concentration was 4.4 mmol/L. The urinalysis showed no evidence of nitrate or pyuria, and the urine culture showed no growth. His chest radiograph showed no evidence of definite pneumonic consolidation. We could not perform a diagnostic ascites tapping because the patient's ascites was very small. After the preliminary assessment of hospital-acquired infection and a blood culture examination, the patient was treated with piperacillin/tazobactam, ciprofloxacin and intravenous fluid. The central venous pressure became 12 mmHg, but the systolic blood pressure remained at 80 mmHg. Therefore, we started an infusion of dobutamine (10 µg/kg/min), dopamine (25 µg/kg/min) and norepinephrine (100 µg/min) through the central venous catheter in the right subclavian vein. Due to anuria subsequent to the exacerbated azotemia caused by the septic shock, we began continuous veno-venous hemodialysis (CVVHD).

Although norepinephrine was being infused for about 26 hours, the patients systolic blood pressure remained at 80 mmHg and the mean arterial pressure was also intractably low. The skin necrosis did not develop before vasopressin was administered. We began infusion with vasopressin (40 units mixed with 40 mL of normal saline, and then 0.02 unit/min) through the central venous catheter in the right subclavian vein. The systolic blood pressure increased to 120 mmHg, and the mean arterial pressure increased to 80 mmHg.

After the four hours infusion of low-dose vasopressin, the patient developed multiple purpura on both wrists and both lower legs. In time, the region of skin necrosis expanded to both arms, both thighs and the whole abdomen. At that point, the skin lesions progressed to extensive superficial erosion with variably sized bullous lesions (Figure 1). We assessed the erosion as low-dose vasopressin induced skin necrosis and then after 22 hours we discontinued the infusion of low-dose

vasopressin. So we didn't perform biopsy or culture of the skin lesions.

*Escherichia Coli* growth was confirmed by the blood culture. Despite the continuous infusion of dobutamine and norepinephrine, the patient died due to hemodynamic instability.

## DISCUSSION

Low-dose vasopressin is being rapidly incorporated into the treatment for septic shock, and although there have been a few reports on safety of low dose vasopressin, vasopressin needs more clinical experience or trials in respect to patients with septic shock. When patients with septic shock develop necrotic skin lesions, the mortality rate is usually very high<sup>12</sup>. To the best of our knowledge, this case is the first report on severe skin necrosis that developed in a vasodilatory septic shock patient after an infusion of low-dose vasopressin through a central venous route. In an earlier report on skin necrosis due to a peripheral infusion of low-dose vasopressin, the authors found that this condition was caused by vasopressin extravasation into the soft tissue<sup>10</sup>.

Vasopressin is one of the most important endogenous stress hormones that are released during shock<sup>13</sup>. The serum vasopressin concentrations increase significantly at the early stage of septic shock, and they become inappropriately low with respect to the degree of hypotension during the late stage of septic shock<sup>1</sup>. Inappropriately low serum concentrations of vasopressin contribute to the development of hypotension during sepsis. At the same time, septic shock is accompanied by an increased sensitivity to exogenously administered vasopressin<sup>14</sup>. Therefore, infusions of 0.01~0.04 units/min vasopressin in septic shock patients increase the plasma vasopressin concentrations. This increase is associated with an increased systemic vascular resistance and arterial blood pressure that consequently reduces the dosage requirements of adrenergic agents<sup>15</sup>.

The optimal site for vasopressin infusion is not clear. Historically, central venous administration of vasopressin has been avoided due to the myocardial ischemia that results from the coronary artery vasoconstriction<sup>4-6</sup>. This complication has been reported in connection with high-dose vasopressin infused to patients with gastrointestinal hemorrhage. There is little evidence that infusions of low-dose vasopressin can cause myocardial ischemia by central administration. Nevertheless, there has been two case reports on skin necrosis resulting from peripheral intravenous administration of low-dose vasopressin in the treatment of patients with catecholamine-resistant septic shock<sup>10, 11</sup>. This observation suggested that for patients who are given low-dose vasopressin for catecholamine-resistant septic

shock, skin necrosis induced by a peripheral infusion of low-dose vasopressin could be avoided by administration of the infusion through a central venous catheter.

However, in our case, low-dose vasopressin may have caused severe skin necrosis in connection with its administration through the central venous catheter, even without extravasation into the soft tissue. As to this patient, we provide several explanations for the skin lesions. First, the cutaneous manifestation may have been a feature of the bacteremia, which was due to such bacteria as *staphylococcus* and/or *pseudomonas*<sup>16</sup>. We could not completely exclude that systemic bacteremia had caused the skin lesions in our patient. However, the necrotic skin lesions developed after four hours of the vasopressin infusion, and there was no extension of the skin lesions after we discontinued the vasopressin infusion. Moreover, these lesions were similar to previously reported skin lesions that developed in connection with high-dose and low-dose vasopressin<sup>8-12</sup>. We presume that the necrotic skin lesions were caused by the low-dose vasopressin infusion rather than by *Escherichia Coli* bacteremia. Second, we considered the potential role of norepinephrine in the pathogenesis of necrotic skin lesions. Typically, skin necrosis due to norepinephrine appear on the fingertips or the tiptoes. On the other hand, vasopressin induces skin necrosis at the sites of extravasation or on the muscular parts of the limbs. In our patient, although the norepinephrine infusion was being administered for 26 hours, in the meantime no skin lesions were noted to develop. Furthermore, there was no evidence of necrosis on the toes or the fingertips, and skin lesions were noted on the muscular parts of the limbs. So we think that the possibility that the skin necrosis might have been associated mainly with norepinephrine is not high. Third, the patient received CVVHD during the vasopressin therapy. Therefore, there is a doubt about the vasopressin dose in this case being a really low-dose, in combination with the anuria and CVVHD. However, vasopressin has a short half life, and it is metabolized mainly by the liver. Renal clearance seems to be a minor pathway. Although there have been no reports on using vasopressin in patients with anuria and CVVHD, we were sure that the kidney dysfunction could not be taken into account in this patient.

Thus, we suppose that vasopressin might have been associated with the skin necrosis. While the exact mechanism of skin necrosis due to vasopressin is unknown, systemically induced vasoconstriction is a plausible explanation. A recent retrospective study has indicated that the risk factors for high-dose vasopressin (4~6 u/hr) induced skin necrosis include a high body mass index, preexisting peripheral arterial occlusive disease, presence of septic shock and high norepinephrine requirements<sup>12</sup>. Our patient might have had multiple risk factors

for vasopressin induced skin necrosis.

To the best of our knowledge, this is the first published case showing that low-dose vasopressin induced severe skin necrosis even by the central route administration. Although treatment of septic shock patients with low-dose vasopressin may control their hypotension, the possible development of complications such as skin necrosis in connection with the central venous catheter employed for infusion suggests that in septic shock patients with many risk factors, low-dose vasopressin should be used with great caution.

## REFERENCES

- 1) Mutlu GM, Factor P. *Role of vasopressin in the management of septic shock. Intensive Care Med* 30:1276-1291, 2004
- 2) Dunser MW, Mayr AJ, Ulmer H, Knotzer H, Sumann G, Pajk W, Friesenecker B, Hasibeder WR. *Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. Circulation* 107:2313-2319, 2003
- 3) Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Lery MM. *Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med* 32:858-873, 2004
- 4) Gimson AE, Westaby D, Hegarty J, Watson A, Williams R. *A randomized trial of vasopressin and vasopressin plus nitroglycerin in the control of acute variceal hemorrhage. Hepatology* 6:410-413, 1986
- 5) Davison R, Kaplan K, Bines A, Spies S, Reed MT, Lesch M. *Abnormality thallium 201 scintigraphy during low-dose vasopressin infusions. Chest* 90:798-801, 1986
- 6) Sirinek KR, Levine BA. *High-dose vasopressin for acute variceal hemorrhage: clinical advantages without adverse effects. Arch Surg* 123:876-880, 1988
- 7) Greenwald RA, Rheingold OJ, Chiprut RO, Rogers AI. *Local gangrene: a complication of peripheral Pitressin therapy for bleeding esophageal varices. Gastroenterology* 74:744-746, 1978
- 8) Korenberg RJ, Landau-Price D, Penneys NS. *Vasopressin-induced bullous disease and cutaneous necrosis. J Am Acad Dermatol* 15:393-398, 1986
- 9) Mogan GR, Wormser GP, Gottfried EB. *Infected gangrene: a serious complication of peripheral vasopressin administration. Am J Gastroenterol* 73:426-429, 1980
- 10) Kahn JM, Kress JP, Hall JB. *Skin necrosis after extravasation of low-dose vasopressin administered for septic shock. Crit Care Med* 30:1899-1901, 2002
- 11) Bunker N, Higgins D. *Peripheral administration of vasopressin for catecholamine-resistant hypotension complicated by skin necrosis. Crit Care Med* 34:935-936, 2006
- 12) Dunser MW, Mayr AJ, Tur A, Pajk W, Barbara F, Knotzer H, Ulmer H, Hasibeder WR. *Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: incidence and risk factors. Crit Care Med* 31:1394-1398, 2003
- 13) Holmes CL, Walley KR. *Vasopressin in the ICU. Curr Opin Crit Care* 10:442-448, 2004
- 14) Novak F, Lubanda H, Onderkova R, Zak A. *Vasopressin and its analogues in the therapy of shock. Cas Lek Cesk* 143:307-312, 2004
- 15) Delmas A, Leone M, Rousseau S, Albanses J, Martin C. *Vasopressin and terlipressin in septic shock patients. Crit Care* 9:212-222, 2005
- 16) Mandell GL, Bennett JE, Dolin R. *Principles and practice of infectious diseases. 6th ed. p. 1186-1189, United States of America, Elsevier, 2005*