Skin Necrosis after High Dose Vasopressor Infusion in Septic Shock

Two Case Reports

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Survival sepsis campaign recommends that vasopressor therapy is required to maintain mean arterial pressure (MAP) ≥ 65 mmHg. However, the absolute maximum dose of vasopressor is difficult to determine. Herein, we report 2 cases of severe skin necrosis after high dose vasopressor infusion to maintain the recommended MAP in septic shock. In our first case, norepinephrine 1.0—2.0 μg/kg/min and vasopressin 0.03—0.1 U/min were infused for 5 days; in the second case, dopamine 10—20 μg/kg/min and norepinephrine 0.25—2.5 μg/kg/min were infused for 7 days. Severe ischemic skin lesions, which required amputations, developed in both cases. The clinical appearance of the skin lesions in the 2 cases was different because of the unique distribution of target receptors for different vasopressors. Thus, when high dose vasopressors are required to achieve recommended MAP, extra vigilance is required. Further studies for dose adjustment are needed.

Key Words: gangrene, septic shock, vasoconstrictor agents.

An international effort to improve the conditions that arise from severe sepsis and a septic shock resulted in the publishing of “Survival Sepsis Campaign: International guidelines for management of severe sepsis and septic shock”.[1] They recommend that vasopressor therapy is required to maintain mean arterial pressure (MAP) ≥ 65 mmHg. Dopamine and norepinephrine are recommended as the first choice vasopressors for the management of hypotension in septic shock and epinephrine as the second line agent whereas vasopressin may be effective in patient refractory to other vasopressors. However, they did not mention the maximum dose of vasopressors for the maintenance of MAP ≥ 65 mmHg. Because of the wide variability in vasopressor usage nationally and internationally and in individual vasopressor requirement, the absolute maximum dose of vasopressor is difficult to determine. In general, when starting vasopressors, their doses should be titrated to the desired effect by closely monitoring the adverse effects. We report here 2 cases of severe skin necrosis after high dose vasopressor infusion for the maintenance of MAP ≥ 65 mmHg in patients with septic shock, which showed very different results. This report discusses how high dose vasopressor infusion affects the progress of septic shock and patient’s quality of life after the recovery.

CASE REPORT

1) Case 1

A 39 year old man with diagnosed testicular cancer was admitted for scrotal pain and the aggravation of general condition. On the day of admission, diuretics were administrated because the patient presented with oliguria. On the third day in the hospital, he developed hypotension (60/40 mmHg), tachycardia (125 beats/min), tachypnea (40 breaths/min), and hypoxemia (SpO2 88%). In accordance with the Surviving Sepsis Campaign guidelines, he was treated with fluid resuscitation.
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Fig. 1. There are vasopressin-induced ecchymosis and bullous skin lesions on the left hand and both thighs and calves (A, B), whereas dry gangrene induced by norepinephrine appear on the fingertips and toes (C, D).

Afterward, his central venous pressure (CVP) was 15 mmHg but hypotension persisted. Norepinephrine infusion was started at a dose of 1.0 μg/kg/min through the central venous catheter in the subclavian vein. Mechanical ventilation and continuous veno-venous hemodialysis were initiated.

Although norepinephrine was infused for 17 hours and the dose having been increased up to 2.0 μg/kg/min, his MAP level still remained indicative of hypotension. We began an infusion of vasopressin 0.03 U/min through the central venous catheter and increased the dose up to 0.1 U/min on the same day. After a 9-hour infusion of vasopressin and 26-hour infusion of norepinephrine, he developed multiple ecchymosis and bullous lesions on the chest and scrotum and peripheral cyanosis. Laboratory examinations revealed disseminated intravascular coagulation (DIC). The ecchymosis and bullous skin lesion on the chest and scrotal area expanded to both thighs and calves for two days (Fig. 1A, B), and ischemic change of both fingers and toes became aggravated (Fig. 1C, D). After 72 hours, vasopressin and norepinephrine infusions were ceased since his septic condition improved. Despite the cessation of vasopressors, the development of extensive skin gangrene and gross fluid exudation on the fingers and the lower limbs of the patient worsened. The orchiectomy and amputation of all fingertips and feet was planned, but was refused by his guardian. One week later from orchiectomy, he died of cancer progression and the recurrence of septic shock.

2) Case 2

A 40 year old man without medical history, who had a right hand crushing injury and undergone reimplantation 2 weeks previously, was admitted to our hospital and preliminarily diagnosed with septic shock. After endotracheal intubation, he was transferred to the intensive care unit (ICU). On the first day in the ICU, arterial blood pressure was 80/50 mmHg, heart rate 100–130 beats/min, and CVP 14–16 mmHg despite fluid resuscitation. Norepinephrine (0.25–2.5 μg/kg/min) and dopamine (10–20 μg/kg/min) infusions were started through the central venous catheter in the subclavian vein. Continuous veno-venous hemodialysis was also applied due to acute kidney insufficiency (AKI).

72 hours after the infusion of vasopressors, he began to show cyanosis at distal areas of both fingers and toes. On the sixth
day, dopamine and norepinephrine infusions were discontinued since his septic condition improved. However, ischemic lesion at the distal areas of both fingers and toes were aggravated, eventually leading to the necrosis of the lesions (Fig. 2A−C). Laboratory examinations for vasculitis and autoimmune disease were all negative. DIC was confirmed by laboratory examinations but CT angiography of the upper and lower extremities showed no evidence of vascular occlusion.

Laboratory abnormalities and renal function recovered 1 month after his admission. He underwent an amputation of the right arm below elbow as required for the removal of septic sources. After the formation of a line of demarcation, left 2nd, 3rd, 4th, 5th fingers and all toes were amputated (Fig. 2D−F). Nine months later from his hospital admission, he was discharged. Amputation of all toes caused him a great disturbance in rapid gait, spring, squatting and tiptoeing. Therefore, he had to wear shoe fillers on both feet for the enhancement of resilience and received rehabilitation training afterward.

**DISCUSSION**

Ischemic skin necrosis is a serious complication in critically ill patients with a high mortality rate (up to 40%) and half of survivors require amputation of affected limbs.[2] One of pathophysiologic treatments of ischemic skin necrosis in critically ill patients is known as vasopressors such as dopamine, norepinephrine, and vasopressin.[3-6] Presumptive mechanisms leading to ischemic skin necrosis following the use of vasopressors include extravasation, peripheral administration, and high dose infusion. It is more likely to occur, even with low dose infusion through a central venous catheter,[7] in the presence of risk factors such as sepsis, AKI, obesity, DIC, and pe-
Vasopressors must be used following the Surviving Sepsis Campaign guidelines and its high dose infusion is frequently required in septic shock. Most of septic shock patients have co-morbidities which are risk factors of ischemic skin necrosis. Standard dose ranges of dopamine, norepinephrine and vasopressin infusion are generally known to be 2.0–20 μg/kg/min, 0.01–3.0 μg/kg/min, and 0.01–0.1 U/min, respectively and low dose ranges are known to be safer.[8] In our cases, there was no extravasation and vasopressors were infused centrally through subcalvian vein. However, both cases required high dose vasopressors for several days to maintain adequate MAP levels. In the first case, norepinephrine 1.0–2.0 μg/kg/min and vasopressin 0.03–0.1 U/min were infused for 5 days, whereas, in the second case, dopamine 10–20 μg/kg/min and norepinephrine 0.25–2.5 μg/kg/min were infused for 7 days. Both patients had septic shock, AKI, and DIC. Interestingly, clinical appearances of ischemic skin necrosis in two cases were different. The first case was caused by norepinephrine and vasopressin. Ischemic skin necrosis occurred not only of the fingers and toes, but also on the thighs and calves. Fingers and toes developed dry gangrene, whereas thigh and calves were covered with extensive bruises and large exudative blisters. On the contrary, the second case was caused by dopamine and norepinephrine. Only the fingertips and tiptoes became dry gangrenous. This case was consistent with previous reports that skin necroses due to norepinephrine and vasopressin appear in different areas.[5-7,9] Norepinephrin-induced skin necrosis typically occurs on the fingers and toes, while vasopressin spares them. This is related to the unique distribution of the target receptor of vasopressin, vasopressin receptor type 1 (V1 receptor), which is located in smooth muscles of the blood vessels, mainly in the territory of the splanchnic circulation, kidney, myometrium, bladder, adipocytes, hepatocytes, platelets, spleen, testis and skin circulation.[10] It might be explained by wider areas of skin, such as thighs and calves, which have more V1 receptors and more likely to be affected by vasopressin.[11]

Kingston and Mackey[12] suggested five possible pathomechanisms of skin lesion in septic shock: DIC, direct vascular invasion and occlusion by bacteria and fungi, immune vasculitis and immune complex formation, emboli from endocarditis, and vascular effects of toxins. In the second case, laboratory tests revealed DIC but CT angiographic results of the upper and lower extremities for vascular occlusion were negative. Laboratory examinations for autoimmune disease also showed negative results. However, in the first case, we could not perform imaging tests, wound biopsy nor laboratory exams to rule out other causes of skin necrosis because of the patient’s financial problem. Only DIC was confirmed. Although thorough investigations to rule out other possible causes could not be performed on the patients of the second case either, his septic condition improved without healing of the skin lesions. This meant that skin lesions were not caused by infection. Clinical manifestations of skin necrosis in the second case were consistent with previous reports.[5-7,9] It will be reasonable to assume that skin necrosis was an adverse effect of norepinephrine and vasopressin.

Several studies have reported that the implementation of the Surviving Sepsis Campaign guidelines was associated with a significant decrease in mortality.[13,14] In Spain, a three-year follow-up quasi-experimental study with a historical comparison group found that achieving ScvO2 ≥ 70% within 6 hours was the only single intervention that maintained the predictive value of survival independently of the other interventions.[13] In another study, there was a statistically significant decrease of odds ratio for mortality in patients who had received corticosteroids and in mechanically ventilated patients whose inspiratory plateau pressure becomes < 30 cmH2O within 24 hours.[14] Treatment of hypotension with fluids and vasopressors were not the interventions independent of lower mortality in the both studies. Their impact on mortality in severe sepsis and septic shock has rarely been studied, which is also classified as a low quality evidence (grade C) in Surviving Sepsis Campaign guideline.[1] It is obvious that hypotension must be corrected for adequate tissue perfusion in septic shock. However, when high dose vasopressors are required to achieve the recommended MAP, especially in patients with ischemic skin necrosis risk factors, extra vigilance is also required. We should closely monitor the signs of inadequate skin perfusion and, if needed, may assess the skin microcirculation using non-invasive techniques such as capillaroscopy, laser Doppler flowmeter, and transcutaneous measurement of oxygen tension.[15] Furthermore, prospective studies are needed to suggest guidelines for dose adjustment of vasopressors in patients with septic shock.

REFERENCES


