Ischemic Skin Necrosis in Hepatorenal Syndrome Patient Secondary to Terlipressin

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ABSTRACT
Hepatorenal syndrome and variceal bleeding are two serious complications of chronic liver disease. Terlipressin is commonly used for reversal of these conditions. Besides its clinical advantages, it often causes serious ischemic complications. These complications are seen in patients at risk. Ischemic events, typically involve peripheries, but gastrointestinal mucosa, coronary arteries, trunk, and scrotum are also rarely involved. We observed extensive skin necrosis of right hand and forearm of a 50-year female patient treated with terlipressin for hepatorenal syndrome. Since this event was never noticed earlier in tertiary care hospitals of our province; to the best of authors' knowledge, this is the first case in medical literature from this part of the country.

Key Words: Hepatorenal syndrome, Terlipressin, Ischemic complications.
started at 3 mcg/kg/min as a continuous infusion.

Considering indication of hemodialysis, after written and informed consent, double lumen dialysis catheter was inserted in right femoral line and a gentle session of about two hours was done. Following morning (day 2 of admission), after discussion with consultant nephrologist, terlipressin was advised, initially as a bolus dose of 2 mg intravenous (IV) followed by 1 mg IV (slow peripheral injection) every six-hourly. Along with terlipressin, human albumin was given at a dose of 1 g/kg body weight for 5 days. Norepinephrine was continued because of low blood pressure. Meanwhile, both blood and urine were sent for culture and sensitivity.

Following treatment with terlipressin, her blood pressure improved to normal range. The second session of hemodialysis was done. Despite the above measures, her renal functions did not improve. On the second day of starting terlipressin, she developed extensive cyanosis (dark bluish skin) of her right hand (both dorsal and palmer surfaces) extending proximally to elbow, while distal phalanges of left hand and toes of both feet had a similar appearance. Peripheries were very cold to touch and small bullae were also developing on right forearm. These features developed when the patient has received one bolus dose and six maintenance doses of injection terlipressin. While no other causative factor could be found, these features were attributed to terlipressin and the drug was immediately stopped. Doppler vascular studies could not be done because of the short timeframe between the appearance of cyanosis; and arteriography study was not possible because of acute kidney failure. Meanwhile, during the next session of hemodialysis, she developed severe hypotension and dyspnea leading to cardiac arrest and death.

**DISCUSSION**

Currently, the most effective treatment appears to be vasoconstrictor therapy for reversal of splanchnic vasodilation and restoration of the effective arterial blood volume (EABV) with 5% human albumin infusion (1 g/kg on day 1 up to 100 gm; thereafter, 20 to 40 g/day).¹

Vasopressin analogues (via splanchnic V1 receptors) exhibit preferential vasoconstrictor effect on the splanchnic bed and improve renal circulation.³

Terlipressin is a synthetic analogue of vasopressin that has a greater effect on the vascular vasopressin receptors (V1) than the renal vasopressin receptors (V2). It is a parent drug and is transformed into its active form, lysine vasopressin. Terlipressin has a prolonged half-life and can be given both as an IV injection and an IV infusion.⁴ Though its action is limited to splanchnic vasculature, it also has a vasoconstrictor effect on systemic circulation. Continuous administration improves the probability of HRS reversal and decreases the incidence of systemic ischemic side effects.²,³ Various prospective and retrospective studies in patients with HRS have revealed that terlipressin along with daily albumin infusion resulted in improvement of renal function in 60% of the patients, with 37% survival beyond 1 month.⁵-⁷ One study published recently reported that terlipressin along with albumin prolongs short-term survival of HRS (type-1) patients.⁸ Child-pugh score (<12), and MELD score are independent predictors for survival.⁶ As described previously, our patient had a child-pugh class-C, and a very high MELD score of 36, both signifying poor prognosis.

Adverse ischemic effects of terlipressin, such as skin necrosis, can typically involve distal extremities, scrotum, trunk, and abdominal skin.⁴,⁵ Several risk factors, like history of ischemic heart disease, venous insufficiency, spontaneous bacterial peritonitis, and obesity have been noticed for the development of ischemic complications.⁴ Ischemic events leading to myocardial infarction due to coronary arteries ischemia, intestinal mucosa (bowel necrosis), of breast and genitalia, have also been previously reported as lethal complications.⁴ Notably, ischemic side effects after terlipressin occurred in 4% to 12% of patients.⁴-⁶

Authors believe that the skin lesion observed in the patient occurred as a result of terlipressin therapy. The majority of case reports (as in present report) are related to skin necrosis, typically involving the peripheries,⁴,⁵,⁹ but there is also a small number of case reports of the foreskin and scrotal necrosis in males.¹⁰ Some authors also suggest more risk factors like hypovolemia and concurrently administered pressor drugs for this complication. Ischemic complications as a result of vasoconstrictor medication mostly affect peripheral areas such as the digits of the hands and feet.⁴ In this case, due to hypotension, the patient also received norepinephrine in overlap with the first two doses of terlipressin, increasing the risk of ischemic events. It is also possible that obesity in this patient was an additional risk factor for developing complications. This case suggests that strict monitoring is warranted in administering terlipressin in patients with risk factors like morbid obesity and previous arterial insufficiency.

Treating patients of HRS or variceal bleed with terlipressin is usually found to be a very enthusiastic action, particularly for junior doctors. It might be associated with severe ischemic adverse effects in patients who are at significant risk for ischemic complications. Recognising these risk factors beforehand, an immediate cessation of terlipressin is warranted in these patients because it might help in reducing these complications.

**REFERENCES**


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