Coagulopathy: A Possible Mechanism of Terlipressin-induced Peripheral Ischemic Complications – Evidence from Published Case Reports

Terlipressin, a synthetic analog of vasopressin, was introduced in as early as 1990. It is widely used in the treatment of hepatorenal syndrome and bleeding esophageal varices, but is associated with ischemic and other adverse effects.[1] Although common, the mechanism of these ischemic complications is still unknown. The mechanism of these ischemic complications can be summarized into two hypotheses: vasoconstriction hypothesis and V1 receptor adipose tissue hypothesis.

Being a vasopressin analog, it is hypothesized that the ischemic adverse effects of terlipressin are related to its nonselective stimulation of V1 receptors. Few case reports of terlipressin-induced peripheral gangrene reported normal flow and spectral waveform in all major arteries in Doppler.[2,3] Again, in many cases, fingers and toes were not affected despite affecting the whole limb.[1] Fingers and toes are affected frequently in vasoconstrictor medication-medicated peripheral ischemic complications. Hence, it seems unlikely that vasoconstriction is the sole player in terlipressin-mediated ischemic complications.

Now, coming to V1 receptor adipose tissue hypothesis, many case reports report ischemic peripheral complications, especially in areas with large skin surface and fat, e.g., thigh, breast, and abdominal wall.[4] Some authors have attributed this to greater amount of V1 receptors present in adipose tissue as a responsible factor for ischemic gangrene affecting limbs.[5] Now, coming to normal body physiology, in peripheral limbs, adipose tissue is mainly located in the subcutaneous region of skin. However, in maximum of the cases of terlipressin-induced peripheral gangrene, epidermis and dermis were involved.[1] Subcutaneous tissue was involved in only 16.6% of cases.[1] Again, many of the ischemic complication sites do not have subcutaneous adipose tissue layer, e.g., scrotum.[1] Hence, this finding contradicts the adipose tissue V1 receptor hypothesis.

Another important differential diagnosis of terlipressin-induced gangrene is cutaneous vasculitis, or it can be a manifestation of coagulopathy. In histopathology, a sign of vasculitis was not prominent in most of the case reports. Dermal capillaries also showed thrombosis without inflammatory infiltrate.[6] Again, autoimmune markers were also found to be negative.[3] Hence, a cutaneous autoimmune vasculitis is most unlikely.

Regarding coagulopathy, histopathologically, dermal vessel thrombosis is reported in many cases of terlipressin-induced peripheral ischemic cases.[6-8] Vasopressin and its analogs are reported to release von Willebrand factor (V2 receptor-mediated action) and factor VIII[1,9,10] and which enhances platelet aggregation and subsequently can cause thrombosis.[9,10] Human platelets express typical V1 vascular vasopressin receptors.[11] Vasopressin causes aggregation of human blood platelets.[12] Vasopressin was able to cause aggregation of washed human platelets suspended in buffered saline in the presence of fibrinogen, calcium, and magnesium ions.[12]

The site of ischemic complication is highly variable which ranged from scalp, tongue, scrotum, abdomen, breast, thigh, feet, toes, and forearm,[1] and there was no site special preference. In few cases, the ischemic complication was reversible after stopping of the drug.[1] Again, heparin[13] is reported (the lesions occur due to alteration of the homeostasis between procoagulant and anticoagulant factors) to cause a similar type of cutaneous lesions, any in many cases, which clears up after some days after stopping, but some progress and can be fatal. The histopathologic findings of both terlipressin and heparin-induced cutaneous lesions are similar.[13]

In two case reports, the ischemic lesions cleared after the use of intravenous alprostadil + oral sildenafil in one case and sildenafil alone in another case,[2,14] and it was thought that vasodilation may be the main mechanism. However, till now, we do not find any evidence of vasoconstriction in any of the case reports from Doppler studies.[1] Again, both alprostadil and sildenafil have strong antiplatelet action.[15,16] Hence, antiplatelet action of these agents may be responsible for the improvement of cutaneous lesions.

Hence, to conclude, "coagulopathy" along with "vasoconstriction" seems to be the most likely mechanism of terlipressin-induced ischemic complications [the possible mechanism is shown in Figure 1] in the settings of current

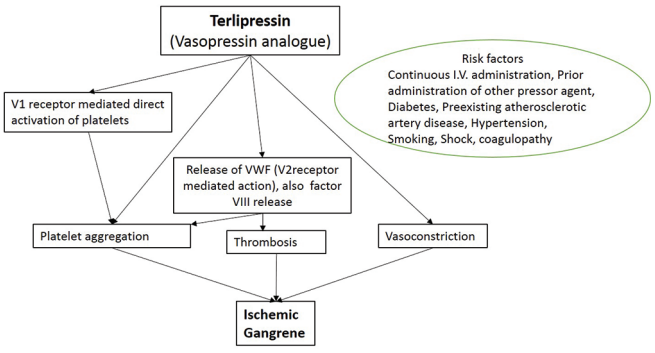

Figure 1: Possible mechanism of terlipressin-induced ischemic complications

evidence. The coagulopathy may be the result of release of Von willebrand factor (VWF) or direct platelet activation by vasopressin, which may be responsible in addition to other factors for the cutaneous necrotic lesions.

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Conflicts of interest

There are no conflicts of interest.

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