Review Article

Terlipressin-Induced Ischemic Complications: A Systematic Review of Published Case Reports

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Abstract

Terlipressin is used in the management of variceal bleeding and hepatorenal syndrome. Ischemic complications are rare, but serious adverse effects of terlipressin therapy can be fatal. In this context, we reviewed all the published case reports of terlipressin-induced ischemic complications, and data were collected regarding the part of body affected by ischemic complication, latency, geographical variation, different treatment strategies and their outcome, and other relevant information. After an exhaustive search in different databases, 33 published cases were found. The ischemic complications affected virtually every part of the body. Peripheral gangrene was the most common ischemic complication followed by ischemic complications of more proximal parts such as thigh and abdominal wall. Other parts affected were heart, colon, small intestine, scrotum, etc. Most cases were managed conservatively. Although in few cases, other treatment options were also explored, knowledge of this dreaded complication and different management strategies is necessary for early identification of this adverse effect and early management so as to prevent fatality.

Keywords: Gangrene, hepatorenal syndrome, ischemic complication, terlipressin, vericeal bleeding

Introduction

Variceal bleeding and hepatorenal syndrome (HRS) often complicate advanced liver disease. Earlier vasopressin was used for the treatment of HRS and variceal bleeding, but it had moderate efficacy and was associated with high rate of ischemic adverse effects.[1] Terlipressin, introduced in the early 1990s, is a synthetic analog of vasopressin with fewer side effects and longer duration of action.[2] Terlipressin is recommended for the management of both the conditions.[2-4] Ischemia leading to gangrene is a relatively rare adverse effect of terlipressin. In this context, we reviewed all the published case reports of terlipressin-induced ischemic complications. This is the first review of this kind for evaluation of different terlipressin associated ischemic complications, management strategies, and their outcome.

Search strategy

We used different permutations and combinations of keywords "terlipressin," "ischemia," "gangrene," "necrosis," "infarction," "case report," and "report" for searching different databases such as PubMed, Embase, Google Scholar, and Cochrane database (till July 22, 2016). In addition, we also searched references of the studies of screened articles to extract information about relevant articles.

Study selection

In the first step, titles and abstracts of the articles were reviewed and irrelevant articles were excluded. In the next step, full texts of the selected articles were screened as per inclusion and exclusion criteria.

Inclusion criteria – (a) patients: any age group and both genders, (b) intervention: terlipression, and (c) type of study: case report. Exclusion criteria: articles with an outcome other than ischemic event were excluded from the study.

Data extraction

The first two authors independently extracted the data. In case of any discrepancy, the last and the penultimate authors were consulted

Access this article online

Quick Response Code:

Website: www.jpharmacol.com

DOI: 10.4103/jpp.JPP_23_18

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How to cite this article: Sarma P, Muktesh G, Singh RS, Mishra A, Singh A, Ruhela RK, *et al*. Terlipressin-Induced ischemic complications: A systematic review of published case reports. J Pharmacol Pharmacother 2018;9:76-85.

Received: 26-02-2018 **Revised:** 30-06-2018 **Accepted:** 05-06-2018

and the issue was resolved. In case full article was not available or it was in other language, data were collected from abstract.

Results

Spectrum of ischemic complications and its outcome

Reports of only 33 cases (from 28 published case reports and case series) could be found in literature [Figure 1 and Table 1]. Ischemic complications affected multiple regions of body including limbs and abdominal wall, heart, gastrointestinal (GI) tract, scrotum, and other miscellaneous body parts (penis, breast, scalp, etc.) The spectrum of ischemic complications are presented in Table 2. Out of the 33 cases, 11 cases recovered, death occurred in 17 cases (1 case showed initial improvement but later died due to complications), and information was not available in 5 cases. Patients across all age groups were affected (2 months–79 years). Both males and females were found to be affected.

Ischemic complications affecting limbs and abdominal wall

In 61% of the cases, ischemic complications affected different part of limbs and abdominal wall [Tables 2 and 3]. Figures 2 and 3a, b shows the spectrum of gangrene affecting different parts of limbs. Among cases showing ischemic complications of limbs and abdominal wall, 13 cases suffered from gangrene involving distal limbs (5 recovered, 6 died, and information could not be retrieved in 2 cases) and 9 cases involved thigh and abdominal wall (1 recovered, 7 died, and information could not be retrieved in 1 case). One case of finger-sparing upper-limb ischemia was also reported. Latency period for manifestation of complications ranged from 2 to 11 days for ischemia affecting limbs and abdominal wall.

Ischemic complications affecting cardiovascular system

Among patients affected by terlipressin-related ischemic complications, 15% had an event which was related to cardiovascular system [Tables 3 and 4]. Till now, five reported cases are found in literature. Among the five reports, one report was in French, so data from only four reports were retrieved. Effects of myocardial ischemic complications ranged from ST depression with normal cardiac enzymes to acute ST-elevated myocardial infarction (MI). It affected both males and females (males = 2 and females = 2) and mainly elderly peoples were affected (45–73 years). The latency to ischemia ranged from 20 min to few hours in case of MI. All the cases showed the presence of risk factors for ischemic heart disease. The risk factors present were diabetes, dyslipidemia, coronary artery stenosis, hypothyroidism, hypertension, and smoking. Most cases were managed conservatively with prompt stoppage of terlipressin, moist oxygen inhalation, nitroglycerin infusion, and other medical management strategies. Percutaneous transluminal coronary angioplasty was performed in one case. Among the four

Table 1: Data on age range affected and gender-wise distribution of reports

Variable	Cases
Total case reports	28
Total cases reported	33
Male	22
Female	6
No information on gender (articles in other language/no information)	5
Age range affected	2 months-79 years

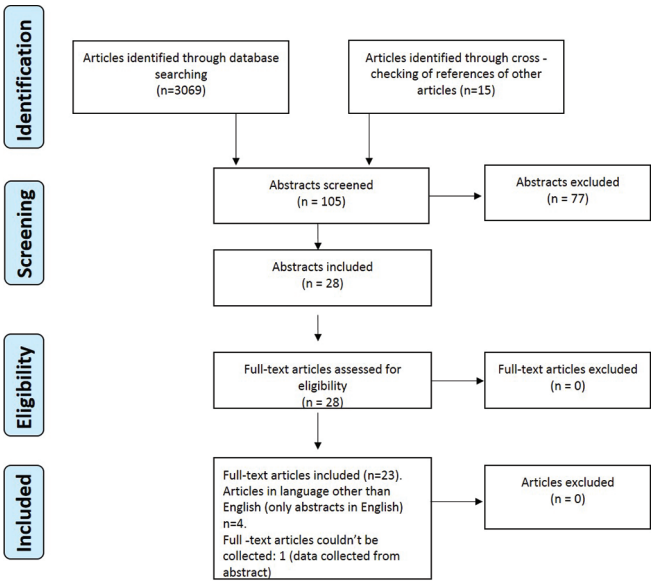

Figure 1: Flow diagram of case reports included in the review

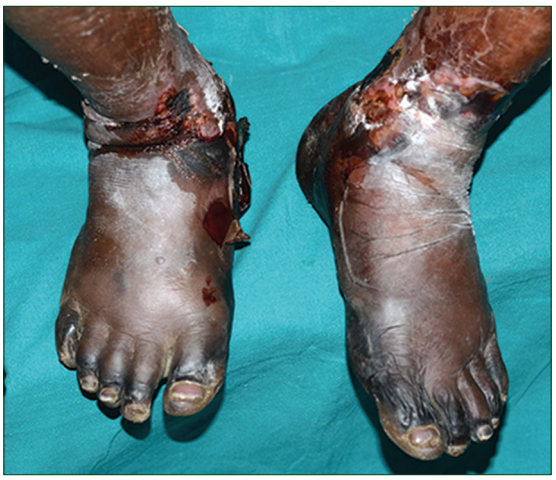

Figure 2: Terlipressin induced gangrene of both legs

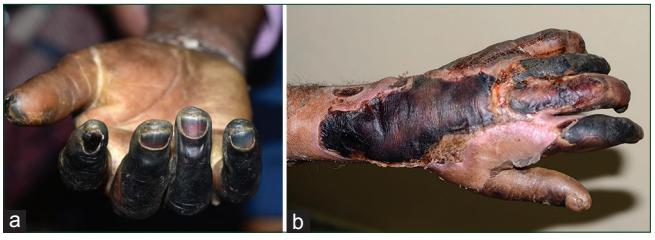

Figure 3: (a and b) Terlipressin induced gangrene of hand

Table 2: Ischemic complications involving limbs, abdominal wall, and other miscellaneous body parts

Year	Age/Gender	Indication	Dose	Ischemic complications	Skin biopsy	Management	Latency	Reference
2014	65/male	Variceal hemorrhage	1 mg IV every 4 h	Areas of erythema, swelling, and bruising on the skin of the extensor side of forearm and hand, sparing the fingers	Nonspecific inflammation extending from the dermis into the subcutaneous fatty tissue. Vascular congestion in the upper dermis. Dermal vessels did not show any sign of vasculitis or thrombus formation	Terlipressin injection was immediately discontinued and the wound on the right forearm was dressed with hydrocolloid solution	2 days/skin graft	[5]
2013	71/male	HRS	1 mg every 4 h	Peripheral gangrene and osteomyelitis	Information not available	Terlipressin was stopped. Regular dressing IV alprostadil 10 µg/day, later oral sildenafil 50 mg every 12 h, but urine output decreased Alprostadil and sildenafil were withdrawn and IV furosemide was introduced	11 days/ maximum ischemia affected part recovered, three toes needed amputation	[1]
2013	47/male	Actively bleeding varices	1 mg 6 times a day	Non blanching bilateral erythematous lesions of the extremities, with areas of ecchymosis and necrosis of the overlying skin	Not performed	Terlipressin was stopped	3rd day/ completely reversible	[6]
2012	79/male	HRS	1 mg IV 4 times a day + albumin	Scrotal skin	Dermal ulceration, necrosis, and nonspecific inflammation	Terlipressin was discontinued	2nd day/died	[7]
2012	65/male	HRS	1 mg IV 4 times a day + albumin	Scrotal skin	N/A	Terlipressin was discontinued	2nd day/died	[7]
2011	47/male	HRS	0.5 mg QDS	Bullous hemorrhagic lesions in legs, spreading to feet and thighs with subsequent gangrene of the left second toe	Epidermal necrosis and ulceration, superficial dermal vessels showed evidence of the presence of fibrin thrombi	Terlipressin was stopped	2 days/died	[8]
2011	53/female	N/A	Information not available	Skin of the abdominal wall and upper thighs developed extensive bruising and blistering	Information not available	Terlipressin stopped	5 day/died	[8]

Contd...

Table 2: Contd...

Year	Age/Gender	Indication	Dose	Ischemic complications	Skin biopsy	Management	Latency	Reference
2011	41/male	Variceal hemorrhage	1 mg QDS IV	Skin of the posterior part of thighs and legs developed ecchymosis and blistering	Presence of subepidermal bulla formation	Terlipressin stopped	3 days/ improved after 2 weeks of stopping terlipressin	[8]
2011	66/male	Upper GI bleed	2 mg every 4 h	Dark-grayish skin lesions on the thighs, calves, and abdomen followed by epidermolysis on the following day. Epidermolysis progressed to other parts of the body, including the arms; sparing the hands and feet. Wide areas of skin were covered with bullaes	Desquamating Epidermal tissue, implying macroscopic bullae were the result of epidermal detachment	Not mentioned	5 days after starting and 2 days after terlipressin discontinued/ died	[9]
2011	51/female	Acute variceal bleeding with kidney injury	4 mg/24 h	Cyanosis of the toes progressed to ischemia extending to the whole feet with extensive tissue damage. Poor peripheral pulses Doppler ultrasound showed features of normal flow with no signs of obstruction	N/A	Terlipressin discontinued immediately, conservative management, but there was no sign of improvement. Oral sildenafil 50 mg BD was started. Sign of improvement was seen from the 3rd day onward. After that, the patient was kept on oral sildenafil 75 mg/day for 2 weeks.	3rd day of treatment/ recovered completely at 1 month	[10]
2010	50/male	HRS	1 mg 8 h IV	Peripheral gangrene in all the four limbs	Information not available	Terlipressin was stopped	2 days/ prolonged ICU stay of 26 days. Other details not mentioned	[11]
2010	54/male	HRS	1 mg/6 h	Skin necrosis (flanks, limbs, and scrootum) and rhabdomyelysis	N/A	Terlipressin was stopped	48 h/died due to sepsis	[12]
2009	45/male	GIT bleeding	Dose not mentioned	Acute muscle infarction	Muscle biopsy: necrotic muscles with no microorganisms detected	Complete bed rest. Patient improved by 5 days	2 days/ recovered completely	[13]

Contd...

Table 2: Contd...

Year	Age/Gender	Indication	Dose	Ischemic complications	Skin biopsy	Management	Latency	Reference
2009	68/male	HRS	1-mg bolus 4 times a day	Development of reticulated erythema in the trunk region Legs, scrotum, and tongue showed purpuric, necrotic, and bullous lesions Tongue showed evidence of ischemic change A week later, lesions in the trunk and scrotum became necrotic	Superficial dermal capillaries showed evidence of thrombosis. Dermis showed mild lymphocytic and neutrophilic infiltration without associated vasculitis Direct cutaneous immunofluorescence was negative	Terlipressin was stopped	3 days/the patient died 3 weeks later from staphylococcal septicemia	[14]
2009	74/M	Sepsis and "pseudohepatorenal" syndrome	Terlipressin 0.5 mg/h infusion + IV albumin	Development of erythematous, macular, purpuric plaque in scalp	Scalp skin biopsy: Dermal capillaries: thrombosis without inflammatory infiltrate Epidermal necrosis	Terlipressin stopped	4 days/died	[14]
2009	39/male	HRS	0.5 mg/4 h	Cyanosis and pain in the acral areas Purpuric lesions in lower legs, which progressed to the development of large necrotizing areas	Necrosis of epidermis and upper part of dermis leading to epidermal detachment and hemorrhage Dermal vessels: number evident of thrombi or vasculitis	Terlipressin stopped	48-72 h/died	[15]
2008	71/male	Variceal bleeding	1 mg every 6 h	Ischemic skin necrosis mainly on the thigh and scrootum	Wall thickening and fibrinoid reaction of vessel and epidermis cleft	Frequent skin dressing	1.5 day/expired	[16]
2008	65/female	HRS	3 mg/day continuous infusion + albumin	Burning pain in breasts followed by extensive bilateral cyanosis on the skin of breasts and the skin appeared cold	Nonspecific inflammation extending from the dermis into the subcutaneous fatty tissue along with the presence of vascular congestion in the upper dermis No evidence of thrombi or vasculitic signs in the dermal vessels	Terlipressin was stopped	Few hours/ completely recovered within a few days	[17]
2006	47/male	HRS	Terlipressin 0.5 mg QDS + octreotide + albumin	Development of bullous hemorrhagic lesions in legs, later spreading to feet and thighs. This was followed by necrosis and subsequent fluid exudation	Epidermal necrosis, acute ulceration, and hemorrhage Presence of fibrin thrombi in superficial dermal vessels	Terlipressin was stopped	2 days/died	[18]
2006	53/female	HRS	0.5 mg QDS + octreotide + albumin	Skin of the upper thigh and abdominal wall developed extensive bruising and exudative blisters	No information	Cessation of vasopressors	5 days/died	[18]

Contd...

Table 2: Contd...

Year	Age/Gender	Indication	Dose	Ischemic complications	Skin biopsy	Management	Latency	Reference
2006	53/male	Bleeding esophageal varices	1 mg QDS IV + octreotide	Large areas of ecchymosis and blistering on the skin of the right groin and flank	Subepidermal bulla with no evidence of inflammation	Terlipressin was stopped	3 days/died	[18]
2006	41/male	HRS	Article in Korean	Development of gangrene on toes. Necrosis of infusion site.	Information could not be retrieved	Information could not be retrieved	Information could not be retrieved	[19]
2003	73/male	HRS	Bolus of terlipressin (0.5 mg/4 h) + albumin	Skin of abdomen, lower limbs, scrotum, and penis developed severe ischemic complications	Information not mentioned	Terlipressin was discontinued	After 10 boluses of terlipressin/ ischemic complications improved, but patient died due to renal failure	[20]

IV=Intravenous, N/A=Not available, QDS=Quater die sumendus (four times a day), HRS=Hepatorenal syndrome, GIT=Gastrointestinal tract, ICU=Intensive Care Unit

Table 3: Summary of reported cases of ischemic complication of terlipressin

Variable	Cases	Outcome			Latency	Reference
		R	D	NI		
Total cases reported	33	11	17	5		
Limbs and abdominal wall (61%)						
Gangrene of distal parts of limbs/peripheral gangrene	13	5	6	2	2-11 days	[1,5,6,8,10,11,14, 15,18-21]
Upper-limb ischemia but sparing fingers	1	1	-	-	-	[5]
Thigh and abdominal wall	9	1	7	1	1.5-5 days	[8,9,14,16,18,20]
Heart (15%)						
Ischemic complications of heart	5	3	1	1	20 min to few hours	[21-25]
GIT (18%)						
Colon and small intestine	5	2	1	2	Immediately after bolus to up to 12 h	[26-30]
Tongue	1	-	1	-	3 days	[14]
Miscellaneous						
Scrotum (15%1)	5	-	5	-	1.5-3 days	[7,14,16,20]
Penis	1	-	1	-	40 h	[20]
Breast	1	1	-	-	Few hours	[17]
Scalp	1	-	1	-	4 days	[14]
Associated complications						
Associated osteomyelitis	1	1	-	-	-	[1]
Rhabdomyolysis	1	-	1	-	48 h	[12]
Necrosis of infusion site	1	-	-	1	Not available	[19]
Acute muscle infarction	1	1	-	-	2 days	[13]

R=Recovered, D=Died, NI=No information available, GIT=Gastrointestinal tract

cases, three cases survived and one case died. Presence of risk factors such as preexisting coronary artery stenosis, hyperlipidemia, diabetes mellitus, hypertension, and smoking were common among the sufferers from cardiovascular ischemic complications.

Ischemic complications affecting gastrointestinal tract

Nearly 15% of the affected cases reported an adverse event related to ischemia of gastrointestinal tract (GIT) [Tables 3 and 5]. Mostly reported cases involved ischemia of small and large intestines. Five cases were related to ischemic complications of colon and small intestine (two recovered, one died, and information could not be retrieved in two cases). One case of ischemia affecting the tongue was also reported (patient died). Latency period for manifestation of ischemic complications of GIT ranged from immediately after bolus to 12 h (after two doses 6 h apart). Presence of risk factors for GI ischemia was noted in one case (complete information was available in two cases), which were concomitant shock, use of other vasopressors, and concomitant coagulopathy. Surgery

Table 4: Reported ischemic complications of heart following terlipressin injection

Age	Male/female	Adverse event	Associated comorbidities	Terlipressin administration	Management	R/D	Reference
73	Female	Diffuse ST elevation, hyperkinesia in the anterior and apicoseptal segments of the LV, diagnosed acute STEMI	Diabetes and raised serum cholesterol and triglyceride levels Discrete and calcified coronary artery narrowing with 90% luminal diameter stenosis	IV bolus, loading dose, followed by maintenance	Aggressive medical management, preserved coronary flow, hence coronary intervention was not performed Intra-aortic balloon counterpulsation	D	[22]
45	Female	ST depression LV inferior wall hyperkinesia, with 38% EF with normal cardiac enzymes	Poorly controlled type 2 DM (10 years)	Terlipressin 4 mg IV over 2 min	Moist oxygen inhalation, furosemide, fentanyl, nitroglycerin infusion	R	[23]
52	Male	Diffuse global hyperkinesia of right ventricle and LV, 18% EF. Cardiac complication was followed by gangrene of limbs.	Hypothyroidism Type II DM	4 mg stat then 2 mg IV every 6 h	Conservative medical management	R	[21]
61	Male	ST elevation, septal hyperkinesia, LVEF 65%	Hypertension Smoker	1 mg IV	Medical management and PTCA	R	[24]
-	-	Article in French, information could not be extracted	-	-	-	-	[25]

IV=Intravenous, LV=Left ventricle, LVEF=Left ventricular ejection fraction, DM=Diabetes mellitus, PTCA=Percutaneous transluminal coronary angioplasty, R=Recovered, D=Died, EF=Ejection fraction

Table 5: Reported ischemic complications of bowel following terlipressin therapy

Age	Male/female	Disease	AE	Comorbidities	Terlipressin administration	Management	R/D	Reference
46	Male	HCC with HRS-Type 1	Ischemic bowel necrosis	Hypoalbuminemia (3.6 g/dl)	1 mg IV every 6 h (pain abdomen after 2 doses)	Surgery (patient succumbed to persistent hypotension and metabolic acidosis)	D	[27]
-	-	Gastric ulcer	Segmental ischemic necrosis of cecum	Article in German (limited information retrieved)	Terlipressin given for suspected bleeding and esophageal varices	Gastrectomy, splenectomy, and hemicolectomy	R	[28]
-	-	Bleeding esophageal varices	Ischemic colitis	Article could not be retrieved	-	-		[29]
-	-	Bleeding and esophageal verices	Reversible ischemia of colon and intestine	Article in Danish (limited information retrieved)	-	Recovered fully without the need of intestinal resection	R	[30]
2.5	Female	Septic shock with acute pulmonary edema	Severe ischemia from ileum to rectum	Shock, concomitant administration of other vasopressor drugs, and coagulopathy	20 µg/kg every 4 h (indication: refractory shock)	Exploratory laparotomy	-	[26]

IV=Intravenous, AE=Adverse event, R=recovered, D=Died

was the most common mode of therapy for management of the affected cases. Among the affected cases, one case recovered fully, without the need of intestinal resection.

Miscellaneous

Five cases of scrotum and one case of penis involvement (all died) were also reported. In one case, ischemic complications affected the breast (completely reversible, latency: few hours). Most commonly, multiple parts of body were affected simultaneously [Table 3].

Other complications such as osteomyelitis, rhabdomyolysis/acute muscle infarction, and necrosis of infusion site were also reported [Table 3].

Geographical distribution of case reports

Data regarding geographical location of adverse drug reactions are shown in Table 6. Most of the case reports were from Europe (14 cases) and Asia (13 cases). Only one case was reported from North America (Mexico). No cases have been reported from other continents.

Diagnosis

In most cases, typical clinical presentation (gangrene in case of limb ischemia) and typical features of ischemic heart disease or pain abdomen were the initial symptoms, which led to secondary investigations for evaluation of the etiology of the ischemic complication. Diagnostic tests were directed by respective symptom domain such as, echocardiography for ischemic complications affecting cardiovascular system, X-ray, abdominal ultrasonography, computed tomography abdomen, and exploratory laparotomy for abdominal symptoms. For ischemic complications affecting limbs, skin biopsy and color Doppler were commonly done to assess the conditions of major vessels and rule out other diagnoses. Among patients with peripheral ischemia, three studies evaluated the blood flow patterns of major vessels by using Doppler. All the three studies reported no sign of obstruction and normal flow in major arteries.[5,9,10]

Findings in skin biopsy

Among the cases showing peripheral ischemia, 12 case reports reported skin biopsy findings. The most common features are shown in Table 7. Ischemia commonly affected both epidermis and dermis and sometimes subcutaneous tissue. Necrosis and ulceration of dermis and epidermis, subepidermal bullae, vascular congestion in upper dermis, thrombosis of dermal capillaries, and fibrinoid necrosis were the commonly reported features.

Management of the cases

Most patients were managed conservatively with stoppage of terlipressin, dressing, and management of other concomitant problems [Tables 2, 4, and 5]. Among the patients with peripheral gangrene, one patient underwent amputation of three toes.[1] Another patient with forearm and hand involvement (fingers spared) was treated by skin graft.[5]

Use of sildenafil was reported in two cases.[1,10] In one case, the patient was given both oral sildenafil (50 mg twice daily) and intravenous (IV) alprostidil 10 μg every day.[1] However, the patient developed decreased urine output and the agents were withdrawn. In this patient, maximum ischemia-affected parts recovered, but three toes needed amputation.[1] The other case reported a progressive gradual improvement after initiation of sildenafil.[10]

Management strategies of ischemia affecting heart and GIT are noted in their respective section [Tables 3 and 4].

Table 6: Reports as per geographical location

Continent	Country	Number of cases reported	Reference
Asia	Korea	4	[1,16,19,26]
	India	5	[6,8,11,23]
	Israel	1	[9]
	Taiwan	2	[13,22]
	Qatar	1	[21]
	Turkey	3	[5,7]
Europe	Spain	2	[15,20]
	Italy	2	[17,20]
	Germany	2	[12,27]
	Ireland	3	[18]
	France	4	[14,24]
	Denmark (Danish)	1	[29]
North America	Mexico	1	[10]
No information		2	[25,28]

Table 7: Peripheral gangrene: Common findings in skin biopsy

Parameters (total reported skin biopsy: 12)	Percentage of reports showing this finding (%)	Reference
Epidermal involvement		
Necrosis of epidermis, ulceration	33	[8,14,15,18]
Subepidermal bullae with no inflammation	16.6	[8,18]
Dermis involvement		
Necrosis and ulceration of dermis	16.6	[7,15]
Dermal ulceration, necrosis, and nonspecific inflammation	8.3	[7]
Mild lymphocytic and neutrophilic dermal infiltrate without vasculitis	8.3	[14]
Vascular congestion in the upper dermis	16.6	[5,17]
No evidence of thrombi or vasculitic signs in the dermal vessels	25	[5,15,17]
Thrombosis of dermal capillaries	8.3	[14]
Thrombosis of dermal capillaries without inflammatory infiltrate	8.3	[14]
Fibrin thrombi in superficial dermal vessel	16.6	[8,18]
Wall thickening and fibrinoid reaction of vessel and epidermis	8.3	[16]
Subcutaneous tissue involvement		
Nonspecific inflammation (extending from dermis into the subcutaneous tissue)	16.6	[5,17]

Discussion

Acute variceal bleed is a medical emergency. Management is aimed at controlling the acute hemorrhagic episodes, prevention of rebleeding, and improving morbidity and mortality.[31] Initial management depends on the severity of disease, comorbidities, and availability of endoscopic facility. Pharmacotherapy and endoscopy are the two most common modalities for controlling acute variceal hemorrhage. Pharmacological therapy has an advantage that it requires

relatively less expertise than endoscopy and can be initiated as soon as variceal hemorrhage is suspected, even prior to diagnostic endoscopy.[2] Earlier, vasopressin was used for this purpose. Terlipressin is a synthetic analog of vasopressin with longer activity and fewer side effects.[31]

Terlipressin is converted into lysine vasopressin in circulation by endothelial peptidases cleaving the N-triglycyl residue, resulting in "slow release" of vasopressin. This results in prolonged release of vasopressin (half-life of terlipressin is 6 h, whereas that of vasopressin is only 6 min).[14,32,33] Arteriolar vasoconstriction induced by lysine vasopressin is primarily mediated by nonselective stimulation of vascular smooth muscle V1 receptors.[13,34,35] Vasopressin (and its analogs) also activates V2 receptors on endothelial cells, causing release of von willebrand factor, which enhances platelet aggregation and increases the risk of thrombosis, especially in cases of intense and/or prolonged vasoconstriction.[34]

Ischemic complications are relatively rare adverse effects of terlipressin. Till now, only 33 cases are reported (terlipressin is in use since the early 1990s). Proximal and distal parts of limbs, abdominal wall, heart, bowel, scrotum, penis, and even breast ischemia have been reported. Regarding risk factors associated with terlipressin-induced ischemic complications, various studies mentioned that there was no correlation between the dose of terlipressin administered, length of therapy, and severity of ischemia.[14,36] Mégarbané *et al*., 2009, mentioned few possible risk factors, which may be associated with terlipressin-induced ischemic adverse events, which are mode of administration of terlipressin (continuous IV administration), hypervolemia, and prior administration of other pressor agents.[14]

In our review, we found that ischemic complications were more common in persons with risk factors. Common risk factors for the development of ischemic cardiovascular complications were presence of diabetes, preexisting coronary artery stenosis, dyslipidemia, hypertension, and smoking status.[22-24] Shock, prior use of other vasopressors, and coagulopathy were risk factors associated with the development of ischemic bowel disease.[26]

Anantasit *et al*. evaluated the risk factors of vasopressin use-associated serious adverse events (SAEs) in patients with septic shock (Vasopressin and Septic Shock Trial cohort). They evaluated vasopressin level among SAE and non-SAE patients and found that SAEs were not dose dependent. It suggests that higher vasopressin level and simple pharmacokinetics were not associated with the occurrence of SAEs. They also evaluated genes related to four vasopressin pathways, namely arginine vasopressin receptor 1A (AVPR1a, 3 SNP), arginine vasopressin receptor 1B (AVPR1b, 5 SNP), leucyl/cystinyl amino peptidase (LNPEP, i.e., 237 SNP), and oxytocin receptor (OXTR, 3 SNP) pathway. It was found that there was a significant association between AA genotype of rs28418396 single-nucleotide polymorphism near the arginine vasopressin receptor 1b gene and SAEs.[35] Mechanism of this association remains unknown and it needs further investigation.[35] The study by Anantasit *et al*. was done as a part of safety analysis in septic shock patients who received vasopressin. Hence, pharmacogenomics may play a definitive role in predicting and preventing terlipressin-induced SAEs.

Conclusion

Terlipressin is a time-tested drug for the management of vericeal bleeding. Ischemic complications are serious adverse effects of terlipressin therapy. Proper selection of cases with taking into consideration the presence or absence of risk factors may lead to more safe use of the drug. Regarding medical management of the ischemic complications, sildenafil and alprostidil were used in some cases, but we do not have data from any clinical trial regarding this. We need multicentered dedicated studies for evaluation of risk factors of terlipression-induced ischemic complications and associated biomarkers. We reviewed this dreaded complication of terlipressin so that gastroenterologists and physicians become aware of this complication and diagnose it early and thereby prevent further catastrophic events before it turns into a stage of irreversibility.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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