Sildenafil for Treating Peripheral Ischemia and Gangrene: A Case Report and Review

Miyuki Hsing-Chun Hsieh

National Cheng Kung University College of Medicine <https://orcid.org/0000-0002-7995-7408>

Chi-Lun Tsai

Chi Mei Medical Center

Hui-Chen Su (✉ Michael.maggil@gmail.com)

Edward Chia-Cheng Lai

National Cheng Kung University College of Medicine

Research

Keywords: Sildenafil, peripheral gangrene, digital ischemia

Posted Date: February 28th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-15409/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background

Peripheral gangrene is a clinical condition characterized with digital ischemia of extremities usually seen in patients with sepsis or shock that resulted in a hypoperfusion state. It is not common but often complicated with high mortality rate. Currently, there is no definite treatment for peripheral gangrene which often result in amputation.

Methods

We reported a 74-year-old female case of shock-related peripheral gangrene of both feet who was partially and successfully treated by oral sildenafil with a dose of 50mg twice daily. We also reviewed present evidences regarding effectiveness of sildenafil in managing distal ischemia caused by different clinical conditions.

Results

Except for limited regions which had already shown evident dark discoloration (i.e., the 4th and 5th toe on the right foot) at the time of treatment initiation, all other region of peripheral ischemia significantly improved after systemic oral sildenafil treatment for 7 days. The 4th and 5th toe of the right foot eventually turned into a darker area of necrosis with an obvious margin, in contrast to recovered regions. Literature showed relief of pain and reversal of other ischemic symptoms after a few days to months sildenafil therapy.

Conclusions

In accordance with the reported case and current literature, systemic sildenafil shows great potential in ameliorating peripheral ischemia and gangrene as an off-label drug of choice.

Introduction

Peripheral gangrene is characterized by ischemic and necrotic changes of digital extremities and is mostly associated with failure of microcirculation induced by disseminated intravascular coagulation (DIC) or other causes.(1, 2) Peripheral gangrene is usually presented symmetrically in acral limb and is more likely to be known as symmetrical peripheral gangrene (SPG).(1) SPG is complicated with high amputation rate and mortality.(3) Despite removal of possible causes that inducing or aggravating SPG, no specific effective therapy exists.(4) Pharmacotherapy targeting sympathetic blockade or vasodilation such as prostaglandin analogues and phosphodiesterase (PDE) inhibitors had been applied in the management of digital ischemia or SPG.(3)

Sildenafil, a PDE 5 inhibitor, has shown therapeutic benefit in meliorating peripheral gangrene and digital ischemia from little literature.(5, 6) Its benefit in improving microvascular blood flow is proposed to be contributed to the vasodilatory effect. Besides indications of erectile dysfunction and pulmonary hypertension, emerging evidences have revealed its potential as being a drug of choice in ischemia or gangrene of the extremities. (5–7)

Here, we presented a case of suspected shock-related peripheral gangrene treated by sildenafil. Our aim is to review potential mechanism of sildenafil in treating peripheral gangrene and to investigate the effectiveness of this medication. Clinical use of sildenafil in treating acral ischemia or peripheral gangrene and other conditions such as scleroderma and some autoimmune disorders are discussed as well.

Materials And Methods

Case presentation

A 74-year-old female with hypertension history suffered from back pain due to a fall on Oct 26, 2018. The pain persisted and she was sent to emergency department on Oct 28, 2018. T-L spine x-ray showed T12 compression fracture and the patient was admitted to our ward for further treatment. The patient had been noted for presenting with lower blood pressure (97/61 mmHg) and tachycardia (heart rate 100 beats per minute) on 10/29 with shortness of breath. Dyspnea and hypotension progressed on 10/30–31 and lab tests revealed: random glucose 67 mg/dL, VBG-pH 7.3, VBG-PCO₂ 35.9 mmHg, VBG-PO₂ 49.2 mmHg, VBG-O₂ saturation 79.6%, VBG-Act cHCO₃ 18.3 mmol/L, VBG-ctCO₂ 19.4 mmol/L, VBG-Base Excess – 6.7 mmol/L, VBG-Std cHCO₃ 18.7 mmol/L; BUN 59 mg/dL, Creatinine 2.97 mg/dL, Na 138.9 mmol/L, K 5.09 mmol/L, Albumin 2.0 g/dL; W.B.C. 1.8 10³/uL, Hb 11.0 g/dL, Platelet count 24000/uL, Band 24.8%; lactate 5.0 mmole/L. Septic shock was impressed. We performed endotracheal intubation for the patient and gave fluid resuscitation and applied norepinephrine for unstable hemodynamics. We initiated empirical antibiotic with piperacillin/tazobactam and provided respiratory support for the patient and transferred her to ICU for further care.

During ICU, patient's platelet count further decreased to 5000/uL, suggested an ongoing DIC. Acute kidney injury with metabolic acidosis and systemic edema was also noted; therefore we applied continuous venovenous hemofiltration since 11/01. We added ceftriaxone besides piperacillin/tazobactam due to Salmonella infection being identified. Vasopressin had been added to norepinephrine for low systemic vascular resistance noted on 10/31. Norepinephrine was kept from 10/31 to 11/5 and had been gradually tapered from 10ug/min to 1ug/min. It was discontinued on 11/5 after recovery of blood pressure (134/72 mmHg). Under the use of vasopressors, distal toes of both feet presented with ischemic change and persistent coldness. On 11/06, obvious purple-blue discoloration was developed on right plantar foot (Fig. 1-a, 1-b) while mild discoloration noted on left one (Fig. 1-c, 1-d). Shock with hypoperfusion state and use of vasopressor were thought to be possible causes for digital ischemia of the feet.

Results

Treatment and follow-up

We communicated with the family and decided to try oral sildenafil for treating the ischemia. Sildenafil 50 mg Q12H was administered from 11/07 to 11/15. Among all toes, the 4th toe on the right foot displayed more severe ischemic change which eventually developed into total gangrene despite the treatment (Fig. 2-a, 2-b). There was a limited area (involved the 2nd and 5th toe) on right plantar foot presented with lighter ischemic discoloration and relatively clear margin of the involved region. Other areas of peripheral ischemia significantly improved after use of sildenafil (Fig. 2-b, 2-c, 2-d). Even though the peripheral ischemia of both feet improved significantly, unstable systemic hemodynamics and respiratory pattern forecasted poor prognosis. There was a deterioration of hypotension on 12/05 and the patient deceased.

Discussion

Peripheral gangrene is characterized by distal ischemia without arterial vessel occlusion or vasculitis. It usually presents symmetrically and involved two or more extremities and is more often called symmetric peripheral gangrene (SPG). (8, 9) SPG is mostly associated with failure of microcirculation induced by DIC in patients with septicemia. Infected bacteria that had been reported include Streptococci, Staphylococci, Pneumococci, Pseudomonas and Escherichia coli, etc. (10) It is suggested that bacterial endotoxin might impair the coagulation system and platelet function in peripheral arterioles. (11) Other possible causes of SPG include shock-related hypo-perfusion state, use of certain vasoconstrictive agents, antiphospholipid syndrome, Raynaud's syndrome and diabetes, etc. (11, 12) Though peripheral gangrene is not common, high mortality rate of 40% is noted and approximately half of the survived patients required amputation. (3, 11) Our case had experienced septic shock resulted from Salmonella bacteremia and use of vasopressors had possibly exacerbated the ischemia changes of distal limbs.

Before eventual gangrene develops, former stages of SPG include the initial hypo-perfusion state—which is usually presents as septic shock, and the following ischemia. For the first stage, restoration of peripheral circulatory system is the most important. Timely fluid resuscitation with empirical use of broad-spectrum antibiotics is of gold standard. (12) In addition, vasopressors such as norepinephrine and dopamine are recommended by the Sepsis Campaign guideline as drug of choices to treat shock. However, it had been reported to cause peripheral ischemia under therapeutic dosage range. (13) If not managed properly at the initial stage, erythematous, cold and pallor extremities followed by dusky discoloration of skin would be noted, implying profound ischemia. (12) Once ischemic change is noted, aggravating factors should be identified and rigorous intervention is prompted. Due to shock, our patient was prescribed norepinephrine and vasopressin since the first 2 days after admission, and both agents were discontinued no later than 11/05 due to relatively stable blood pressure. However, dusky discoloration of toes and plantar foot was identified. Shock-related hypo-perfusion and DIC was believed to be the cause of the distal ischemia with vasopressors being an exacerbating factor.

Even though several medications had been proposed in managing peripheral gangrene, no specific effective treatment exists to date. (3, 12) Except for correcting underlying conditions that may cause DIC, different medications which include vasodilators or antithrombotic drugs might be tried according to literature. These include sympathetic blockers such as intravenous chlorpromazine hydrochloride and topical infiltration of phentolamine hydrochloride. Numerous classes of vasodilators such as IV prostaglandins (e.g., epoprostenol) (14), phosphodiesterase inhibitors (e.g., pentoxifylline, sildenafil) (6, 11), endothelin receptor antagonist (e.g., bosentan) (15), IV nitroprusside, IV trimethaphan (16) and topical use of nitroglycerin (17) were all reported with various extent of effectiveness for digital ulceration or peripheral gangrene. Clinical use of anticoagulants, antiplatelets, thrombolytic agents and application of hyperbaric oxygen therapy were also documented. (18) Final and definite management is to perform amputation once demarcation of the necrotic gangrene develops. (1)

Among available treatment options, sildenafil appears to be a relatively effective therapy in the management of peripheral gangrene or digital necrosis. (5–7, 19, 20) Sildenafil selectively inhibits phosphodiesterase 5 (PDE5) and prevents cyclic guanosine monophosphate (cGMP) from breaking down. This results in smooth muscle relaxation in blood vessels. (21) The vasodilating effect of sildenafil promotes microcirculation of blood flow in the digital limbs. Thus, ameliorating acral ischemia under circumstances in which vasospasm is believed to be the etiology. The potential benefits of sildenafil were found from both in vitro and in vivo studies. In animal studies, sildenafil demonstrates angiogenesis in ischemic limbs of mice through protein kinase G-dependent (PKG) pathway. (22, 23) It was found to increase vascular density, promotes

proliferation of endothelial cells and enhances vascular perfusion and tissue blood flow. Furthermore, sildenafil-mediated blood vessel growth was proven dose-dependent in which in vivo incubation of chicken chorioallantoic membranes with larger dose of sildenafil was observed with increasing vascular length.(24) Preliminary human study also revealed sustained protection of endothelial function from ischemia and reperfusion injury under sildenafil dose of 50 mg per day.(25) In addition to vasodilation and improvement in endothelial dysfunction, inhibition of platelet activation was noted following administration of sildenafil and it overall contributed to increased cutaneous capillary circulation in patients with coronary artery disease.(26, 27)

In clinical setting, sildenafil is formally approved with the indication of erectile dysfunction and pulmonary arterial hypertension, taking advantages of its vasodilating effect. In addition, sildenafil is used off-label to improve digital ischemia and ulcerations associated with Raynaud's disease. A meta-analysis with 6 randomized controlled trials have shown that PDE5 inhibitors (sildenafil, tadalafil and vardenafil) present with moderate yet significant improvement in symptoms of secondary Raynaud's phenomenon (RP), included decreased frequency and duration of RP attacks.(28) Other studies disclosed similar therapeutic benefits brought by PDE5 inhibitors.(29) A recent randomized, placebo-controlled trial was designed to investigate the efficacy of sildenafil on ischemic digital ulcer healing in systemic sclerosis.(30) Sildenafil was administered 20 mg three times a day for 12 weeks. The study outcome revealed a favorable healing rate of sildenafil when compared to placebo at week 8 and week 12. However, shortening of healing time was not observed. Side effects resulted in drug discontinuation included drowsiness, syncope, headache, facial, edema and rash. The study results have confirmed clinical benefits of sildenafil.

Taken its potential efficacy, sildenafil was first reported to be applied in sepsis-induced symmetrical peripheral gangrene in 2012.(19) Sepsis-induced vasoconstriction and vasospasm aggravated by vasopressors use shares common presentation of RP in which vasoconstriction is too excessive it becomes vasospasm and is leading to reduction of blood flow and decreased digital perfusion. The authors believed management of RP might help alleviating signs and symptoms of SPG. As a result, sildenafil was provided and it turned out working very well. Apart from this case, more case reports applying sildenafil in managing peripheral ischemia due to different causes have been published. We summarized characteristics of these cases in Table 1. These patients with various ages were mostly female. The causes or exacerbating factors of peripheral ischemia include sepsis-induced low-perfusion status, RP caused by autoimmune diseases such as systemic sclerosis or antiphospholipid antibody syndrome, and few of them were heavy smokers. Nearly all cases manifested with cyanotic change from the digital extremities, i.e., fingers or toes. The peripheral ischemia was accompanied with pain, pallor, cold or swelling. Before sildenafil administration, many patients had tried anticoagulants, antiplatelets, calcium channel blockers, NTG paste or IV prostaglandins but failed. Until sildenafil with a daily dose of 75 to 150 mg usually given in three times per day was provided, the symptoms of digital ischemia became significantly improved in most cases. Most of the patients experienced marked reduction in pain and ischemic symptoms and some of them even avoided amputation. The treatment duration of sildenafil ranged from months to years and all the cases remained with sustained medication effectiveness with mild or no side effects during the follow-up visits.

Table 1
Reported cases applying sildenafil in treatment of peripheral ischemia

NO.	Age	Sex	Clinical condition	Aggravating factors	Peripheral ischemia sign	Treatment	Dose of sildenafil*	Outcome (time after treatment)	Ref.
1	8	F	Cutaneous polyarteritis nodosa	Immune-mediated systemic vasculitis	Raynaud's phenomenon + fingertip ulceration and necrosis	IV steroids, nifedipine, sildenafil, pentoxifylline, nitroglycerin paste, aspirin, LMWH, IVIG	20 mg three times a day	Improve in swelling, discoloration; regained color, perfusion, sensation with residual necrotic distal fingertips (at 2-mon.)	(31)
2	16	F	Thrombotic vasculopathy	Antiphospholipid antibody syndrome	Retiform purpura and digital gangrene of toes	Enoxaparin + IV methylprednisolone + topical NTG paste + nifedipine $\diamond$ sildenafil	20 mg three times a day	Rapid relief of pain; increase in dorsalis pedis pulses and fading of the reticular erythema; gangrene stabilized (day 2)	(32)
3	17	F	Symmetrical peripheral gangrene due to Pseudomonas septicemia	Sepsis, DIC	Dusky cyanosis of both feet with painful symmetrical swelling	Antibiotics + IV fluids + LMWH + PO sildenafil	25 mg twice a day	Marked reduction in area of dusky erythema (day 7)	(19)
4	28	F	Scleroderma/lupus progressed to fibrosing alveolitis	Autoimmune dz, active TB + sepsis	Severe digital arthralgia, vasculitis, and progressive ischemia & gangrene	Iloprost IVF 2 weeks $\diamond$ PO sildenafil	50 mg three times a day	Becoming warm, less painful, and less discolored (day 1)	(5)
5	35	F	SLE with recurrence of Raynaud's phenomenon	SLE with high titer aPLs	Painful acrocyanosis of bilateral hands and feet	IV hydrocortisone + enoxaparin + amlodipine + IV iloprost $\diamond$ increased dose of amlodipine and iloprost + sildenafil	120 mg/day	Gradual resolution of critical ischemia (day 7)	(33)
6	37	F	Cervical rib	Raynaud phenomenon, heavy smoker, oral contraception use	Critical upper limb ischemia with increasing pain	Heparin + IV NTG + morphine $\diamond$ iloprost + vascular bypass $\diamond$ sildenafil	25 mg three times a day	Decrease in pain and granulation tissue (1-week); re-epithelized ischemic fingers (at 1-mon.); improved vasculature permeability (at 2-mon.)	(20)

*The arrow indicates treatment in the order of time.

Abbreviations: ACE, angiotensin converting enzyme; aPL, antiphospholipid; dz, disease; IV, intravenous; mon., month; NTG, nitroglycerine; SLE, systemic lupus erythematosus; PO, orally; wk, week

NO.	Age	Sex	Clinical condition	Aggravating factors	Peripheral ischemia sign	Treatment	Dose of sildenafil*	Outcome (time after treatment)	Ref.
7	42	F	Dermatomyositis and thyrotoxicosis	Autoimmune dz, active TB + sepsis	Raynaud's phenomenon + ischemic digital ulceration	Diltiazem + iloprost IVF $\diamond$ PO sildenafil	50 mg three times a day	Digital circulation & pain improved markedly (day 1)	(5)
8	51	F	Bilateral hand burns as a result of seizure attack	Scleroderma with significant Raynaud's phenomenon	Deep dermal contact burns to the volar aspect of digits in both hands	Antimicrobial barrier silver dressings $\diamond$ sildenafil + debridement and split skin graft	20 mg three times a day	Healed wound with minimal functional issues (at 4-mon.); area of gangrene not fully recovered	(34)
9	51	F	Renal failure secondary to GI bleeding	Sepsis, IV terlipressin	Ischemia and necrosis of toes in the lower extremities	DC terlipressin + PO sildenafil	50 mg twice a day	Rapid reversal (day 3) to final recovery (day 30)	(7)
10	57	M	Primary Raynaud's disease	None	Painful, swollen, left index finger associated with purple discoloration	Nifedipine + aspirin + hydromorphone + digital microscopic sympathectomy $\diamond$ sildenafil	50 mg once daily	Relief of pain and ischemic symptoms (within hours); remained symptom free (at 3-mon.)	(6)
11	62	M	Buttock claudication	Heavy smoker	Severe bilateral buttock ischemia with walking limitation	Statin + antiplatelet + ACE inhibitor + rehabilitation + cilostazol $\diamond$ sildenafil	100 mg once daily	Increased walking distance (2 hour and at 1-mon.) and improved quality of life (at 1-mon.)	(35)
12	76	F	Dermatomyositis + disseminated malignancy	Autoimmune dz	Digital ischemia	Diltiazem + iloprost IVF $\diamond$ PO sildenafil	Not mentioned	Immediate improvement in peripheral pain & ischemia & toe ulcers	(5)
*The arrow indicates treatment in the order of time.									
Abbreviations: ACE, angiotensin converting enzyme; aPL, antiphospholipid; dz, disease; IV, intravenous; mon., month; NTG, nitroglycerine; SLE, systemic lupus erythematosus; PO, orally; wk, week									

By comparison, our case of a 75-year-old female with septic shock who suffered from peripheral ischemia of both her foot had been treated with oral sildenafil 50 mg twice a day. The area of digital gangrene was smaller, and symptoms of ischemia improved after 10-day use of sildenafil. The patient's left foot manifested with greater improvement with acral ischemic discoloration being diminished after treatment. However, although the right foot also showed significant amelioration of the affected plantar area, its 2nd, 4th and 5th toes stayed ischemia with a relatively clear line of demarcation developed especially in the 4th toe displaying total gangrene at last. It might imply better effectiveness if sildenafil therapy is applied at the earlier stage of peripheral ischemia.

Conclusion

This study presented a case and reviewed current evidences that demonstrating potential clinical benefit of sildenafil in improving distal vascular circulation in patients suffered from peripheral gangrene. We highlight the importance of early identifying and removing potential causes of peripheral ischemia. Timely application of oral sildenafil 75–150 mg daily (given in twice or three times) may exert potential benefits in relieving symptoms such as pain and preventing development of further gangrene. Future randomized trials will be required to assure the efficacy of sildenafil, including its optimal time and dosing regimen to treat.

List Of Abbreviations

DIC: disseminated intravascular coagulation

PDE: phosphodiesterase

RP: Raynaud's phenomenon

SPG: symmetrical peripheral gangrene

Declarations

Ethics approval and consent to participate

The legal guardian of the patient (i.e., the son of the patient) gave us permission to review her medical records and publish this study.

Consent for publication

The legal guardian of the patient (i.e., the son of the patient) gave us permission to review her medical records and publish this study.

Availability of data and materials

Due to individual privacy, data sharing is not applicable to this study. The legal guardian of the patient gave consent to only the study authors to access the patient's medical records.

Competing interests

The authors declare that they have no competing interests.

Funding

The authors accept no funding in this study.

Authors' contributions

Ms. Miyuki Hsing-Chun Hsieh organized the patient's clinical information and wrote this manuscript. Doctor Chi-Lun Tsai is the attending who took care of this patient during her hospitalization. Dr. Hui-Chen Su and Edward Chia-Cheng Lai helped review and revise the manuscript.

Acknowledgements

We thank the patient and her family for allowing us to share her clinical information and details and thank nurses of 3BI intensive care unit in Chi Mei Medical Center for documenting photos.

References

1. Ang CH, Koo OT, Howe TS. Four limb amputations due to peripheral gangrene from inotrope use – Case report and review of the literature. *International Journal of Surgery Case Reports*. 2015;14:63-5.
2. Laws JW, Fred HL, Sharp JT, Rabin ER. Multiple peripheral gangrene. *Archives of Internal Medicine*. 1965;115(5):547-51.
3. Jiang J-L, Tseng L-W, Chang H-R. Symmetrical peripheral gangrene in sepsis after treatment with inotropes. *Tzu-Chi Medical Journal*. 2017;29(2):121-4.
4. Shimbo K, Yokota K, Miyamoto J, Okuhara Y, Ochi M. Symmetrical peripheral gangrene caused by septic shock. *Case Reports in Plastic Surgery & Hand Surgery*. 2015;2(3-4):53-6.
5. Kumana CR, Cheung GT, Lau CS. Severe digital ischaemia treated with phosphodiesterase inhibitors. *Ann Rheum Dis*. 2004;63(11):1522-4.
6. Ng WKY, Rosenblatt Y, Brock GB, O'Gorman DB, Siang Gan B. Phosphodiesterase inhibitors in vascular ischemia: A case report and review of their use in ischemic conditions. *The Canadian journal of plastic surgery = Journal canadien de chirurgie plastique*. 2010;18(1):e5-9.
7. Banuelos Ramirez DD, Sanchez Alonso S, Ramirez Palma MM. Sildenafil in severe peripheral ischemia induced by terlipressin. A case report. *Reumatologia clinica*. 2011;7(1):59-60.
8. Tripathy S, Rath B. Symmetric peripheral gangrene: Catch it early! *Journal of Emergencies, Trauma and Shock*. 2010;3(2):189-90.
9. Davis MP, Byrd J, Lior T, Rooke TW. Symmetrical peripheral gangrene due to disseminated intravascular coagulation. *Archives of dermatology*. 2001;137(2):139-40.

10. Molos MA, Hall JC. Symmetrical peripheral gangrene and disseminated intravascular coagulation. *Archives of dermatology*. 1985;121(8):1057-61.
11. Liao CY, Huang SC, Lin CH, Wang CC, Liu MY, Ben RJ, et al. Successful resolution of symmetrical peripheral gangrene after severe acute pancreatitis: a case report. *Journal of Medical Case Reports*. 2015;9.
12. Ruffin N, Vasa CV, Breakstone S, Axman W. Symmetrical peripheral gangrene of bilateral feet and unilateral hand after administration of vasopressors during septic shock. *BMJ case reports*. 2018;2018.
13. Kwon JW, Hong MK, Park BY. Risk Factors of Vasopressor-Induced Symmetrical Peripheral Gangrene. *Annals of plastic surgery*. 2018;80(6):622-7.
14. Denning DW, Gilliland L, Hewlett A, Hughes LO, Reid CD. Peripheral symmetrical gangrene successfully treated with epoprostenol and tissue plasminogen activator. *Lancet (London, England)*. 1986;2(8520):1401-2.
15. Ambach A, Seo W, Bonnekoh B, Gollnick H. Low-dose combination therapy of severe digital ulcers in diffuse progressive systemic sclerosis with the endothelin-1 receptor antagonist bosentan and the phosphodiesterase V inhibitor sildenafil. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG*. 2009;7(10):888-91.
16. Parmar MS. Symmetrical peripheral gangrene: a rare but dreadful complication of sepsis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2002;167(9):1037-8.
17. Gibbs NM, Oh TE. Nitroglycerine ointment for dopamine induced peripheral digital ischemia. *Lancet (London, England)*. 1983;2(8344):290.
18. Ghosh S, Bandyopadhyay D. Symmetrical peripheral gangrene. *Indian Journal of Dermatology, Venereology, and Leprology*. 2011;77(2):244-8.
19. Gandhi V, Sharma R, Raizada A, Dhawan A. Peripheral Symmetrical Gangrene Treated with Sildenafil Citrate. *Journal of Cutaneous and Aesthetic Surgery*. 2012;5(1):57-8.
20. Krahenbuhl SM, Depairon M, Faure M, Vietti Violi N, Applegate LA, Raffoul W. Sildenafil as a therapeutic option for digital ischemic ulceration: case report. *The Journal of hand surgery*. 2015;40(5):890-3.
21. Ghofrani HA, Osterloh IH, Grimminger F. Sildenafil: from angina to erectile dysfunction to pulmonary hypertension and beyond. *Nature reviews Drug discovery*. 2006;5(8):689-702.
22. Sahara M, Sata M, Morita T, Nakajima T, Hirata Y, Nagai R. A phosphodiesterase-5 inhibitor vardenafil enhances angiogenesis through a protein kinase G-dependent hypoxia-inducible factor-1/vascular endothelial growth factor pathway. *Arteriosclerosis, thrombosis, and vascular biology*. 2010;30(7):1315-24.
23. Senthilkumar A, Smith RD, Khitha J, Arora N, Veerareddy S, Langston W, et al. Sildenafil promotes ischemia-induced angiogenesis through a PKG-dependent pathway. *Arteriosclerosis, thrombosis, and vascular biology*. 2007;27(9):1947-54.
24. Pyriochou A, Zhou Z, Koika V, Petrou C, Cordopatis P, Sessa WC, et al. The phosphodiesterase 5 inhibitor sildenafil stimulates angiogenesis through a protein kinase G/MAPK pathway. *Journal of cellular physiology*. 2007;211(1):197-204.
25. McLaughlin K, Lytvyn Y, Luca MC, Liuni A, Gori T, Parker JD. Repeated daily dosing with sildenafil provides sustained protection from endothelial dysfunction caused by ischemia and reperfusion: a human in vivo study. *American journal of physiology Heart and circulatory physiology*. 2014;307(6):H888-94.
26. Halcox JP, Nour KR, Zalos G, Mincemoyer RA, Wacławski M, Rivera CE, et al. The effect of sildenafil on human vascular function, platelet activation, and myocardial ischemia. *Journal of the American College of Cardiology*. 2002;40(7):1232-40.
27. Park JW, Mrowietz C, Chung N, Jung F. Sildenafil improves cutaneous microcirculation in patients with coronary artery disease: a monocentric, prospective, double-blind, placebo-controlled, randomized cross-over study. *Clinical hemorheology and microcirculation*. 2004;31(3):173-83.
28. Roustit M, Blaise S, Allanore Y, Carpentier PH, Caglayan E, Cracowski JL. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomised trials. *Ann Rheum Dis*. 2013;72(10):1696-9.
29. Alekperov RT, Ananyeva LP, Korzeneva EG, Cheremukhina EO. [Efficacy and safety of sildenafil in patients with systemic scleroderma]. *Terapevticheskii arkhiv*. 2013;85(5):60-7.
30. Hachulla E, Hatron PY, Carpentier P, Agard C, Chatelus E, Jegou P, et al. Efficacy of sildenafil on ischaemic digital ulcer healing in systemic sclerosis: the placebo-controlled SEDUCE study. *Ann Rheum Dis*. 2016;75(6):1009-15.
31. Williams VL, Guirola R, Flemming K, Modi GM, Rosales C, DeGuzman MM. Distal extremity necrosis as a manifestation of cutaneous polyarteritis nodosa: case report and review of the acute management of a pediatric patient. *Pediatric dermatology*. 2012;29(4):473-8.
32. Gonzalez ME, Kahn P, Price HN, Kamino H, Schaffer JV. Retiform purpura and digital gangrene secondary to antiphospholipid syndrome successfully treated with sildenafil. *Archives of dermatology*. 2011;147(2):164-7.
33. Levy O, Maslakov I, Vosco S, Markov A, Amit-Vazina M, Tishler M. Critical peripheral ischemia precipitated by severe episode of Raynaud's phenomenon in a patient with aPL-positive systemic lupus erythematosus, upon high titer anti-RNP seroconversion. *Lupus*. 2015;24(3):327-30.

34. Cordova LZ, Schrale R, Castley A. Sildenafil Therapy in Patients With Digital Burns and Raynaud's Syndrome. Journal of burn care & research : official publication of the American Burn Association. 2018.

35. Omarjee L, Camarzana A, Henni S, Abraham P. Nonrevascularizable buttock claudication improved with Sildenafil: A case report. Medicine. 2017;96(8):e6186.

Figures

Figure 1

On 11/06, obvious purple-blue discoloration was developed on right plantar foot (Fig. 1-a, 1-b) while mild discoloration noted on left one (Fig. 1-c, 1-d). Shock with hypoperfusion state and use of vasopressor were thought to be possible causes for digital ischemia of the feet.

Figure 2

Among all toes, the 4th toe on the right foot displayed more sever ischemic change which eventually developed into total gangrene despite the treatment (Fig. 2-a, 2-b). There was a limited area (involved the 2nd and 5th toe) on right plantar foot presented with lighter ischemic discoloration and relatively clear margin of the involved region. Other areas of peripheral ischemia significantly improved after use of sildenafil (Fig. 2-b, 2-c, 2-d).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Patientsinformconsent.pdf](#)