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CASE REPORT

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The effect of topical nitroglycerin on symmetrical peripheral gangrene in a pediatric patient

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Abstract

Symmetrical peripheral gangrene is a rare condition associated with significant morbidity and mortality. The use of topical nitroglycerin may have a role in improving patient outcomes and opens a new area for future research regarding the use of topical nitroglycerin in SPG.

1 | BACKGROUND

Symmetrical peripheral gangrene (SPG) is a rare clinical syndrome first described by Hutchinson in 1891.[1] It is a subtype of purpura fulminans that can be defined as symmetrical distal ischemic damage in two or more extremities without evidence of vasculitis or occlusion of major vessels.[1-4] The ischemic changes usually occur in fingers or toes but can also involve lips, ear lobules, nose, and external genitalia.[2,3] Unfortunately, the exact pathophysiology of SPG is not well understood. However, some theories might correlate it to the Schwartzman reaction, bacterial endotoxin release, and platelet plugging causing a blood flow blockage at the microcirculation level.[1] This phenomenon is usually triggered by disseminated intravascular coagulation (DIC).[1] Among patients with SPG, limb amputation and mortality occur in up to 50% and 40% of patients, respectively.[5,6]

The causes of SPG can be classified into infectious and noninfectious.[1] The noninfectious causes may be due to cardiovascular diseases, connective tissue disorders, malignancy, the use of vasoactive drugs, or hematological diseases.[1,7] *Neisseria meningitidis* is the most commonly recognized infection associated with SPG and purpura fulminans in children, whereas *Streptococcus pneumoniae* is the most common cause in adults.[8]

To date, there is still no definite treatment for SPG. The mainstay part of therapy focuses on treating the underlying cause or removing the aggravating factor.[9] Different types of vasodilating agents had been described in the management of digital ischemia or SPG without conclusive results.[5] Here, we present a child with SPG secondary to refractory cultures-negative septic shock treated by topical nitroglycerin 0.2%.

2 | CASE PRESENTATION

An 18-month-old boy, previously healthy, had otitis media, for which he was given amoxicillin. However, over a few days, he became progressively lethargic and unwell for which he was brought to the emergency department. His symptoms included fever, vomiting, diarrhea, decreased activity, and decreased feeding for 4 days. The condition continued to worsen, and he developed signs of distributive shock 10 hours after the ward admission. Aggressive fluid resuscitation (reaching 60 mL/kg) and broad-spectrum antibiotics were initiated immediately. He was then transferred to the pediatric intensive care unit (PICU) with a picture of cold hypotensive shock with blood pressure been monitored continuously via the femoral arterial line. Epinephrine infusion started peripherally within the first hour of PICU

admission, then switched centrally after central venous catheter insertion. Advanced hemodynamic monitoring using an Ultrasonic Cardiac Output Monitor (USCOM) confirmed a high systemic vascular resistance index. The patient was intubated and mechanically ventilated as his level of consciousness started to decrease due to an ongoing shock state and low brain perfusion condition. Epinephrine infusion was titrated up to a maximum of 0.25 mcg/kg/min, and norepinephrine infusion was also titrated to a maximum of 0.25 mcg/kg/min. Both failed to control the hypotension, as evident by arterial pressure monitoring and poor perfusion state. Most of the other differential diagnoses were excluded at that time, including macrophage activating syndrome and sepsis-induced cytokine storm (his ferritin level was 261 ng/mL). Considering adrenal insufficiency as a sequelae of septic shock state, hydrocortisone (dose of 1 mg/kg/dose every 6 hours) was started with a minimal effect on blood pressure or perfusion. Then, vasopressin infusion was initiated with a rapid withdrawal of norepinephrine infusion. The hemodynamic status began to improve once we reached the vasopressin infusion rate of 0.7 mU/kg/min. All the superficial and deep bacterial cultures and viral testing including blood, urine, cerebrospinal fluids, nasopharyngeal swabs for SARS-CoV-2 and other respiratory viruses, and Bronchoalveolar lavage cultures were negative. Serum SARS-CoV-2 IgG was positive with a negative IgM result. In view of patient presentation and clinical condition, septic shock could not be ruled out and the suspicion of culture-negative septic shock was considered.

His septic shock was complicated with profound DIC and acute respiratory distress syndrome (ARDS). His creatinine, urea (Table 1), and echocardiogram were all normal.

TABLE 1 Summary of patient's laboratory tests results

Test [unit]	Day 0 (admission)	Day 3	Day 5	Day 8	Day 10	Reference range
WBC [x10^9]	4.2	25	30.2	14.2	10.7	6-16
Neutrophil [%]	74.4	79.6	82.4	75.5	77.6	20-40
Hemoglobin [g/L]	93	110	86	105	99	111-141
Platelet count	145	20	29	83	277	200-550
Urea [mmol/L]	5.2	6.9	6.9	2.1	4.1	1.8-6.4
Creatinine [µmol/L]	38	66	43	26	15	35-62
Albumin [g/L]	21	18	22	21	23	35-48
ALT [IU/L]	187	201	260			10-60
AST [IU/L]	233	137	178			10-42
Prothrombin time (PT) [s]	33.5	29.2	18.1	20	17.7	11.5-16
Activated partial thromboplastin time (APTT) [s]	39.7	53.8	41.1	29.1	29.6	23.1-38.7
International normalized ratio (INR)	2.71	2.31	1.33	1.4	1.3	NA
D-Dimer [ng/mL]	6730	9133	17 187		10 559	<255
Fibrinogen [g/L]	6	2.3	1.3	1	1.6	1.8-4.8
Lactate [mmol/L]	3.53					0.5-2.2
C-Reactive Protein (CRP) [mg/L]	267	297	169	62		0-8
Procalcitonin (PCT) [ng/mL]	2161	500	535	388		0.02-0.046
Erythrocyte sedimentation rate (ESR) [mm/h]	65					0-20
Ferritin [ng/mL]	261	1323	493	328		11-150
pH	6.9					7.35-7.45
pCO_2 [mm Hg]	78					35-45
HCO_3 [mmol/L]	17.1					22-26

Six hours post-PICU admission, skin pallor was noticed over the distal aspect of the patient's fingers and toes on all extremities, as well as petechial rash over the palms and soles (Figure 1). These changes were noticed a while before starting vasopressin infusion. Radial and posterior tibial pulses in all limbs were detected using a Doppler device which raises the diagnosis of SPG adding more complexity to the case. Rapid weaning of vasoactive infusions in a stabilizing phase of shock carries a high risk of sudden deterioration with possible mortality. On the other hand, continuing with these high levels of infusions might worsen the SPG condition. As a response, vasoactive infusions were titrated to the lowest possible rate while maintaining hemodynamics. Unfortunately, specific investigations for thrombosis are not available in our center and were not done. Due to the urgency of the situation, heparin infusion was started aiming to control the potential development of the microthrombi. Vasoactive drugs were gradually tapered down until all were discontinued on day 4. Since the third day of his PICU stay, he was in low setting of the mechanical ventilator as his ARDS condition improved. A Magnetic resonance imaging of the brain was performed on day 3, and revealed bifrontal meningeal enhancement with associated areas of tiny hemorrhagic foci, suggestive of meningitis, and bilateral cerebellitis. Although all bacterial cultures failed to grow an organism, culture-negative septic shock remained the main working diagnosis due to the clinical presentation and the previous use of antibiotic prior to hospital admission. Shock-related hypoperfusion and DIC (suggested by low platelet count, elevated D-dimer level, and prolongation of clotting times) were thought to be the cause of his symmetrical gangrene of both hands and feet. Table 1 summarizes the patient's laboratory results during his PICU stay.

Topical nitroglycerin 0.2% was started within 24 hours of noticing SPG with a dose of 4 mm/kg applied as a thin ribbon for each limb every 8 hours. It was applied 5-10 mm proximal to the demarcation line to ensure adequate absorption by surrounding healthy tissue. Blood pressure and methemoglobin levels were closely monitored. As a result, an improvement in skin color was noticed in all limbs within 24 hours of the first application (Figures 2 and 3). There was a continuous improvement in the discoloration in both hands and feet (Figure 4). However, unfortunately, the patient passed away on day 10 of the illness due to complete airway obstruction secondary to massive blood clots, confirmed by an urgent diagnostic and therapeutic bronchoscopy which failed to open the airway.

3 | DISCUSSION

Symmetrical peripheral gangrene can lead to significant morbidity and is associated with an increased risk of mortality when observed in patients with shock.[5,6] Early recognition and intervention are crucial components in the management of SPG. Here, we demonstrate a temporal improvement in tissue perfusion and skin discoloration using topical nitroglycerin in a case of SPG secondary to DIC and septic shock.

Due to the rarity of the condition, there is no definitive treatment for SPG which raises the immediate need for a multi-disciplinary team approach once SPG is suspected.[1] Therapeutic approaches aim to manage the underlying offending factor either by treating the underlying cause, control of contributing factors, or prevention of secondary bacterial infections. No drug has been shown to improve

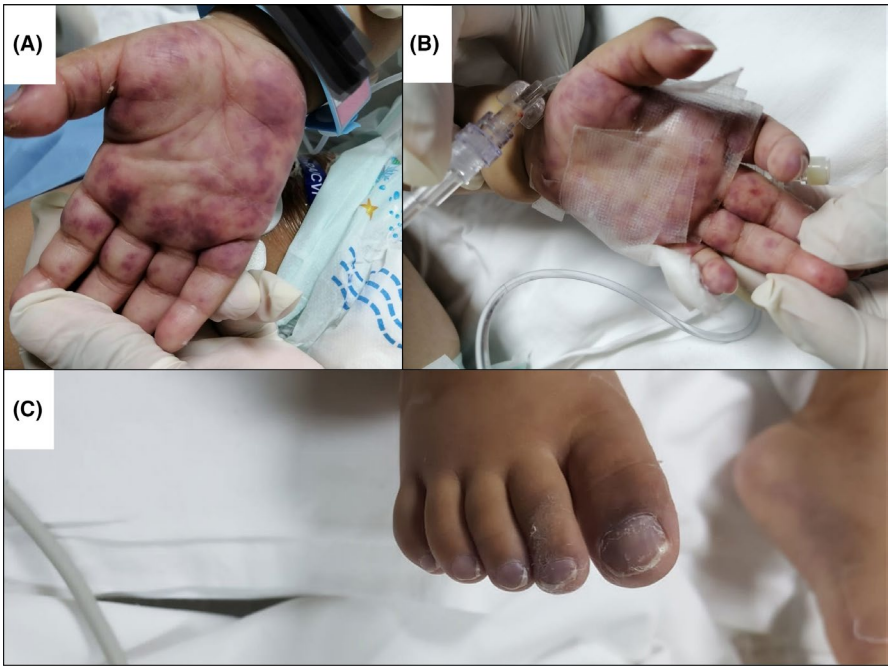

FIGURE 1 The palms of right A, and left B, hands and right toes C, of the patient, 6 h after intensive care unit admission

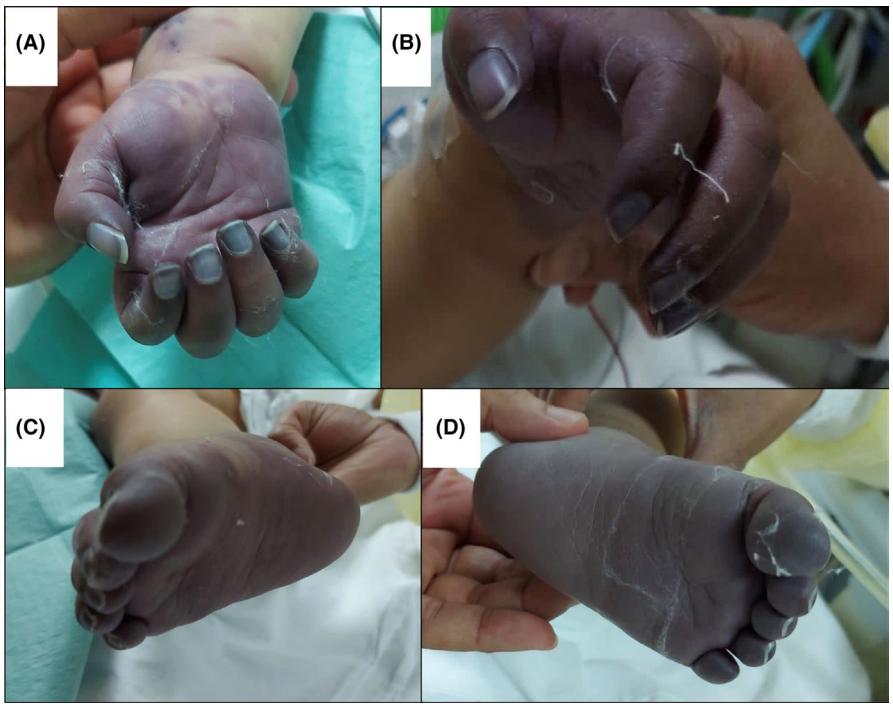

FIGURE 2 The patient's hands A & B, and feet C & D, on the second day of admission to the intensive care unit (prior to nitroglycerin treatment)

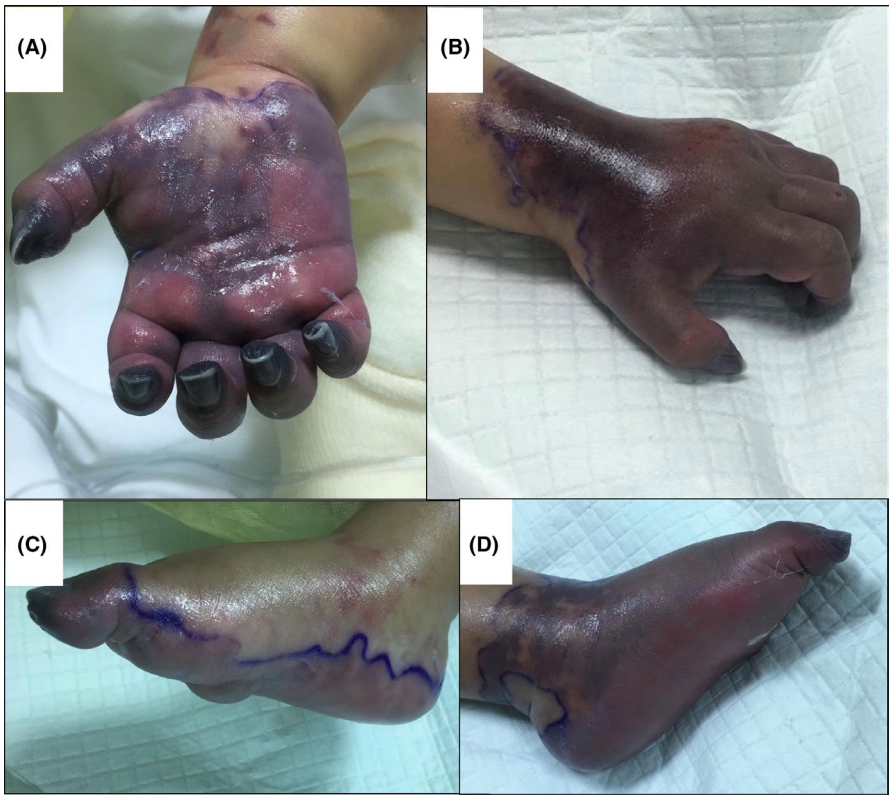

FIGURE 3 The hands A & B, and feet C & D, of the patient, 24 h after the onset of topical nitroglycerin application. The pictures show demarcation of skin discoloration

mortality in DIC definitively.[10,11] A meta-analysis suggested that heparin use in patients with septic shock and infection-related DIC may be associated with a mortality reduction rate of 20%.[12] Former SPG stages include the initial hypoperfusion state followed by tissue ischemia which eventually led to gangrene formation. For the first stage, the restoration of the peripheral circulatory system is the most important intervention.

The exact pathogenesis of how SPG occurs is not well understood. The possible hypothesis includes a low blood flow state as a result of or in association with DIC.[13] Molos et al[14] noted DIC as an essential underlying factor in 85%

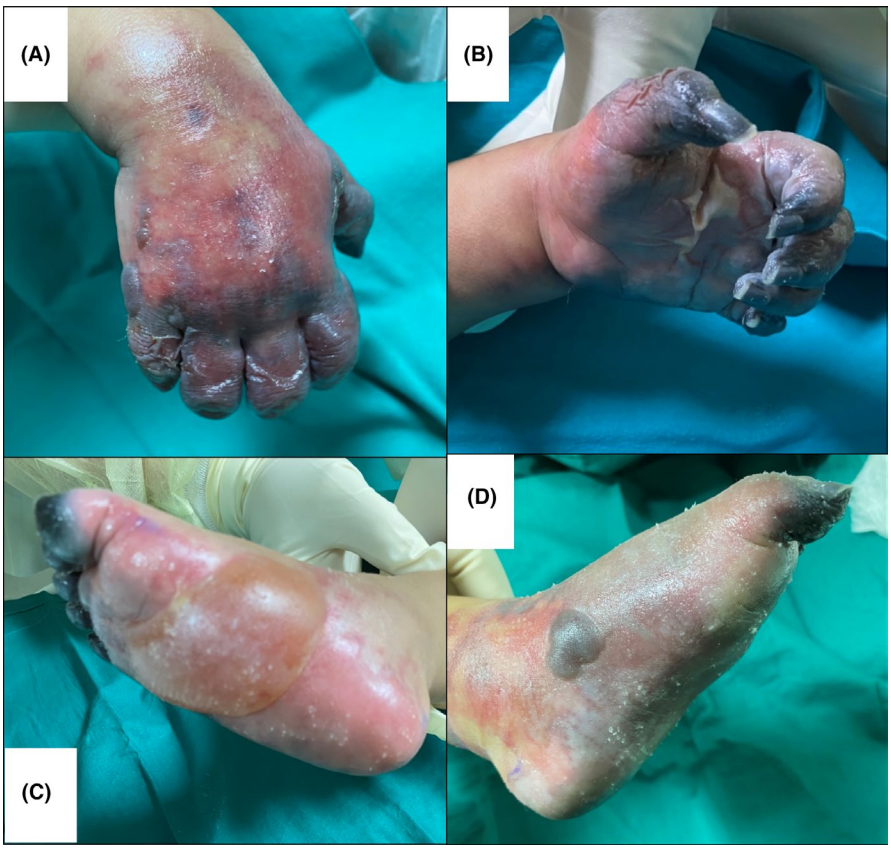

FIGURE 4 The hands A & B, and feet C & D, of the patient, 1 wk after the start of topical nitroglycerin application

of patients who develop SPG. Rarely, SPG can occur in the absence of DIC.[8] SPG might begin as petechial lesions due to capillary dilatation and red-cell extravasation with signs of fibrin deposition and microvascular necrosis. These petechial lesions merge over time to form hemorrhagic bullae in regions of ischemic necrosis.[8,10] Critically ill patients with SPG have increased mortality compared to those without SPG, and a high risk of limb amputations in those fortunate enough to survive.[10]

Some reports described the use of vasodilator agents to improve tissue perfusion in areas affected by SPG. These agents include intravenous (IV) prostaglandins, phosphodiesterase inhibitors, endothelin receptor antagonist, IV nitroprusside, IV trimethaphan, and topical nitroglycerin.[6,15-18] They were all reported with the various extent of effectiveness for digital ulceration or peripheral gangrene. Amputation, as a last resort, may be inevitable once the line of demarcation of the gangrene is developed.[19]

Among available treatment options, topical nitroglycerin appears to be a relatively effective therapy in managing peripheral limb ischemia. Although there was limited evidence supporting any treatment for SPG, some neonatal case reports were advocating the use of topical nitroglycerin with a promising outcome without reporting any side effect.[20,21] Nevertheless, it has been used in the prevention of skin flap necrosis and the management of diabetic ulcers.[22,23] Topical nitroglycerin selectively inhibits phosphodiesterase-5 (PDE5) and prevents cyclic guanosine monophosphate (cGMP) from breaking down. Working on these pathways leads to smooth muscle relaxation in blood vessels. The vasodilating effect of topical nitroglycerin promotes microcirculation of blood flow in the digital limbs. Topical nitroglycerin is well absorbed through intact skin, delivering the highest dose to the area directly beneath. However, the amounts of nitroglycerin reaching the circulation vary in relation to the surface area size and the amount of ointment applied.[24] The onset of action is within 1 hour, and the hemodynamic effects last up to 6 hours. Frequent application over a large skin surface area can potentiate systemic effects of topical nitroglycerin and results in hypotension.

Indications regarding the use of topical nitroglycerin varied in children. In recent years, evidence has been published on nitroglycerin's efficacy to treat ischemic complications associated with vascular cannulation or drug extravasation.[20] The use of topical nitroglycerin in children is limited due to the lack of consensus on its safety and the proper dosage in pediatrics. The side effects of nitroglycerin may include hypotension and methemoglobinemia. In our case, we closely monitored the patient's blood pressure and methemoglobin level, while using topical nitroglycerin 0.2%. We did not observe any adverse effects. Although the available data on topical nitroglycerin is limited to the case series description, the outcomes are promising.

4 | CONCLUSION

We reported a case that had marked improvement in SPG in response to topical nitroglycerin. Further studies are required to test the real effectiveness of topical nitroglycerin in cases of early peripheral ischemia.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

AA: contributed to conceptualization, methodology, data curation, writing—original draft, and supervision. ME: contributed to conceptualization, methodology, data curation, writing—original draft. MA: contributed to conceptualization, methodology, writing—review and editing. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ETHICAL APPROVAL

We confirm that written consent for the publication with obtaining and publishing photographs of the affected body sites during hospitalization of the patient was obtained from the child's parents.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

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