



Noradrenaline Extravasation Management in the Absence of Phentolamine: A Case Series

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ABSTRACT

Noradrenaline (norepinephrine) extravasation can lead to tissue ischemia due to its vasoconstrictive properties. Phentolamine is the preferred treatment but is often unavailable in many Malaysian healthcare facilities. Alternative treatments, such as topical glyceryl trinitrate (GTN) and terbutaline injections, have limited data supporting their use. This case series reports two instances of noradrenaline extravasation successfully managed with terbutaline injections and extemporaneously prepared topical GTN in an Emergency Department setting. These cases highlight the effectiveness of terbutaline and GTN as viable alternatives, providing valuable insights for emergency care in settings where phentolamine is not accessible.

Keywords: Noradrenaline Extravasation; Phentolamine; Terbutaline Injection; Topical GTN

INTRODUCTION

Noradrenaline, an alpha-adrenergic agonist, can induce tissue ischemia and necrosis through vasoconstriction if extravasation occurs. Phentolamine, a nonselective and reversible alpha-antagonist, effectively counteracts the vasoconstrictive effects of extravasated noradrenaline and is the only pharmacological treatment approved by the United States Food and Drug Administration (FDA) for this condition (Lexicomp, 2024a). However, phentolamine is not included in the Malaysian Ministry of Health Medicines Formulary and is unavailable in most local healthcare facilities. Limited data support the use of alternatives like topical glyceryl trinitrate (GTN) and terbutaline injections (Plum & Moukhachen, 2017; Raman *et al.*, 2024). This case series documents two instances of noradrenaline extravasation successfully managed with terbutaline injections and extemporaneously prepared topical GTN in the Emergency Department of a tertiary hospital where phentolamine was not available.

CASE SERIES

Case 1 (Figure 1):

A 56-year-old male patient was administered an intravenous infusion (IVI) of noradrenaline (8 mg in 50 ml normal saline, rate = 2 ml/hour) to manage decompensated heart failure with cardiogenic shock. Eight hours into the infusion, the patient reported pain at the left cubital fossa, the site of the infusion. The cannula was promptly removed. The extravasation area, approximately 9x9 cm in size, was warm and tender but did not show signs of tissue necrosis. An hour later, a 4x4 cm blackish discoloration appeared on the affected skin. Due to the unavailability of phentolamine and commercial glyceryl trinitrate (GTN) ointment in our facility, a decision was made to use alternative treatments. Following consultation with the emergency physician and the emergency medicine (EM) pharmacist, terbutaline

was administered, and the Non-Sterile Pharmaceutical Production Pharmacy was contacted to prepare extemporaneous GTN ointment. The patient received terbutaline (1 mg in 10 ml normal saline, infiltrated around the extravasation site) and GTN 0.5% ointment (applied to the affected area three times daily). Subsequent pain relief was noted, and the skin discoloration did not worsen following the treatment.

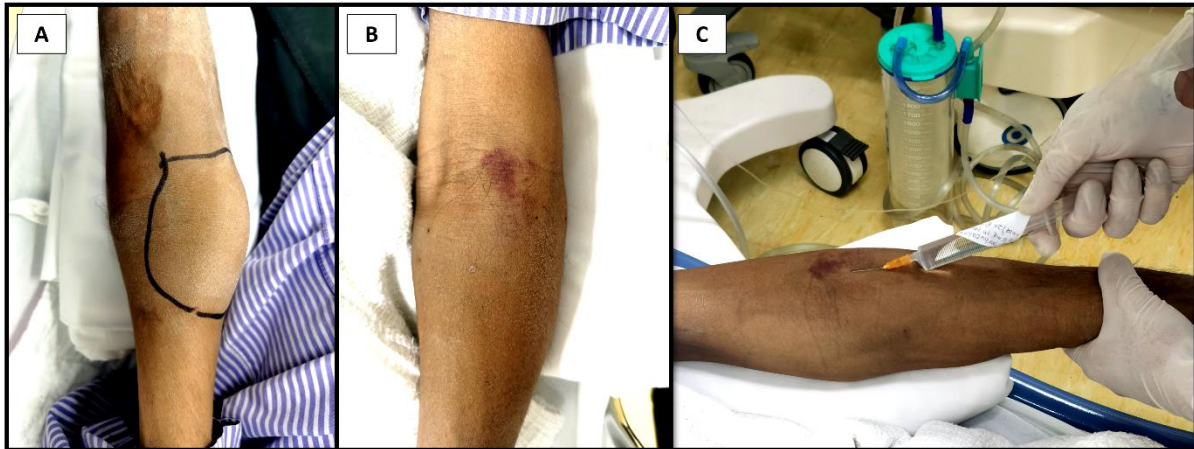


Figure 1: Noradrenaline Extravasation in Case 1 - (A) Extravasation Area after Cannula Removal; (B) Blackish Skin Discoloration Developed 1 Hour after Cannula Removal; (C) Infiltration of Terbutaline around the Extravasated Area

Case 2 (Figure 2):

A 65-year-old male patient, admitted for breakthrough seizures and suspected reactivation of pulmonary tuberculosis, was started on an intravenous infusion of noradrenaline (8 mg in 50 ml normal saline, rate = 1-2 ml/hour) to address hypotension through a left external jugular vein (EJV) access. Fourteen hours later, the patient reported pain in the left neck. Examination revealed a significant subcutaneous swelling in the left neck and anterior upper chest, though there was no skin discoloration. The patient was treated using the same protocol as in Case 1, involving terbutaline and extemporaneously prepared GTN ointment. Following the initiation of treatment, pain alleviated without signs of tissue ischemia. The patient recovered well and was discharged after a two-day hospital stay.

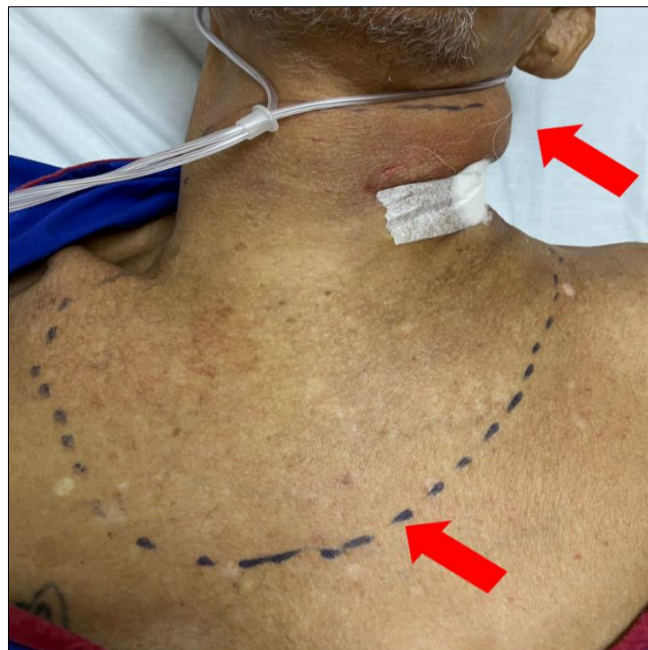


Figure 2: Large Subcutaneous Tissue Swelling Developed over the Left Neck and Anterior Upper Chest Following Noradrenaline Extravasation in Case 2

DISCUSSION

Recognition of high-risk patients, appropriate cannulation techniques, and monitoring of high-alert medications are the standard of care for preventing extravasation injury (Reynolds *et al.*, 2014). In the case of extravasation injuries, prompt interdisciplinary action is often necessary as different drug extravasations have different treatment approaches. In vasopressor extravasation, phentolamine, the preferred treatment of choice, is unavailable in most hospitals. Thus, identifying effective alternatives and early treatment of vasopressor extravasation is crucial to reduce any devastating complications.

Terbutaline injection and topical GTN have been suggested as alternative pharmacological management of vasopressor extravasation in the absence of phentolamine, with most evidence derived from case reports (Plum & Moukhachen, 2017). The local infiltration of terbutaline has been shown to improve peripheral ischemia in cases involving dopamine and dobutamine extravasation over the arm and accidental digital injection of adrenaline (epinephrine) (Stier *et al.*, 1999). This is the first case series that reported the use of terbutaline injection in noradrenaline extravasation cases from the cubital fossa and EJV cannulation sites. Terbutaline is a selective beta₂-agonist. Stimulation of beta₂ receptors by terbutaline dilates the beta₂-mediated vasoconstriction in the peripheral vasculature and increases blood flow to the affected area (Lexicomp, 2024b).

GTN is an organic nitrate that forms free-radical nitric oxide (NO). In smooth muscle, NO activates guanylate cyclase that increases guanosine 3'5'-monophosphate (cGMP), leading to dephosphorylation of the myosin light chains, which causes vascular smooth muscle relaxation. GTN causes both venous and arterial dilation, with a more prominent effect on the veins (Lexicomp, 2024c). A study has reported complete symptom resolution from the combination of topical 2% GTN and phentolamine in 19 cases of vasopressor extravasation involving noradrenaline and dopamine (Cardenas-Garcia *et al.*, 2015). The effectiveness of topical 2% GTN, without concomitant phentolamine, was also demonstrated in neonates and adults, albeit the symptom resolution was much delayed in several cases (Plum & Moukhachen, 2017). In our setting, another challenge is the unavailability of the commercial GTN 2% ointment in most local facilities. In these two cases, GTN ointment was extemporaneously prepared by the Non-Sterile Pharmaceutical Production Pharmacy using GTN tablets and white soft paraffin (Paraffin Mole Alba). One thousand tablets of GTN (0.5mg) were used to prepare 100g of GTN 0.5% ointment for one patient. The maximum achievable concentration for the extemporaneously prepared GTN ointment was only 0.5% due to the significant weight from one thousand GTN tablets. Despite the much lower concentration of GTN ointment used in the cases described above, the combined use with terbutaline infiltration successfully prevented any complications from noradrenaline extravasation.

In addition to pharmacological interventions, non-pharmacological interventions are essential in managing vasopressor extravasation to alleviate symptoms and minimize further complications. These include immediate discontinuation of the vasopressor infusion, gentle aspiration of extravasated solution or any remaining fluid in the catheter before cannula removal, elevation of the extremity, and application of dry warm compresses (Lexicomp, 2024d; Plum & Moukhachen, 2017).

CONCLUSION

Our case series added to clinical experience in the current literature on the management of noradrenaline extravasation. Early identification and appropriate management of noradrenaline extravasation are crucial to prevent serious adverse outcomes. In the absence of phentolamine and commercial GTN 2% ointment, local infiltration of terbutaline and extemporaneously prepared topical 0.5% GTN can be an effective alternative treatment for noradrenaline extravasation.

Conflict of Interest

The authors declare that they have no competing interests.

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