Journal of Veterinary Emergency and Critical Care

WILEY

CASE REPORT OPEN ACCESS

Phentolamine Infusion for the Treatment of Norepinephrine Extravasation in a Dog

Grace E. Flynn | Cody I. Riffe | Kathleen M. Aicher | Lance R. Wheeler

Department of Small Animal Clinical Sciences, College of Veterinary Medicine & Biomedical Sciences, Texas A&M University, College Station, Texas, USA

Correspondence: Grace E. Flynn (grace.flynn@tamu.edu)

Received: 23 September 2024 | **Revised:** 2 March 2025 | **Accepted:** 11 March 2025

Funding: The authors received no specific funding for this work, including no support in the form of grants, equipment, or drugs.

Keywords: alpha-adrenergic receptor antagonist | antihypertensive | catheter site inflammation | catheter site phlebitis | Regitine | vasopressor

ABSTRACT

Objective: To describe a case of clinically significant norepinephrine extravasation in a dog with a successful outcome following the use of subcutaneous phentolamine infusion.

Case Summary: An 8-year-old male neutered Labrador Retriever experienced norepinephrine extravasation from a cephalic, peripheral intravenous catheter while under anesthesia for an exploratory laparotomy. Upon recognition of norepinephrine extravasation, moderate subcutaneous edema and a painful dermal plaque were apparent at the extravasation site. Ten milligrams of phentolamine mesylate, a potent alpha-adrenergic receptor antagonist, were diluted in 10 mL of sterile saline and administered subcutaneously in small aliquots at multiple sites in the area of extravasation. The patient remained hemodynamically stable during and after the infusion. Most phentolamine injections produced instantaneous erythematous macules that resolved 24–36 h later, and the integument in the extravasation area rapidly changed from a "blanched" to a "pink" color. The subcutaneous edema gradually resolved within 7 days post-extravasation. At 12 h following extravasation, the dermal plaque progressed into a necrotic focus, which later developed into an ulcer (36 h), then a small crust (7 days), and finally healed epidermis (9 days). When the patient was euthanized 10 days after surgery due to continued decline secondary to systemic disease, there remained only a small superficial crust at the site of extravasation.

Unique Information: To the authors' knowledge at the time of submission, this case report documented the first reported clinical use of subcutaneous phentolamine infusion for the management of norepinephrine extravasation in a veterinary species.

1 | INTRODUCTION

Norepinephrine is the most commonly used vasopressor for patients experiencing septic shock in human and veterinary medicine [1, 2]. Norepinephrine is a potent alpha-1 and alpha-2 adrenergic receptor agonist and is a moderate beta-1 receptor agonist [2]. The resultant effect of the alpha-adrenergic receptor activation is profound peripheral vasoconstriction [2]. Extravasation of norepinephrine and other vasopressors has been reported to cause local tissue ischemia and necrosis due to their potent vasoconstrictive effects [3]. In order to reduce the risk of vasopressor extravasation, human guidelines traditionally recommend administering norepinephrine through a central venous catheter (CVC) rather than a peripheral intravenous catheter (PIVC) [3]. When treating patients with septic shock, the 2021 Surviving Sepsis Campaign Guidelines

Abbreviations: CRI, continuous rate infusion; CVC, central venous catheter; PIVC, peripheral intravenous catheter.

suggest administering vasopressors through a PIVC in order to restore blood pressure as quickly as possible rather than delaying initiation until a CVC is placed [4]. Should it be necessary to administer vasopressors through a PIVC, human guidelines recommend using a PIVC that is ≥20 gauge for ≤4 h [5].

Phentolamine is a potent, short-acting, alpha-adrenergic receptor antagonist that is the only Food and Drug Administration-approved treatment for norepinephrine extravasation in human medicine [3, 6]. Phentolamine opposes vasoconstriction caused by the extravasation of the majority of alpha-adrenergic vasopressors, such as epinephrine, dobutamine, dopamine, norepinephrine, and phenylephrine [6]. The drug label for norepinephrine bitartrate 1 mg/mL solution for injection has a black box warning providing instructions for phentolamine administration as the "Antidote for Extravasation Ischemia" [7]. According to both the norepinephrine black box warning and current human literature, the vasopressor extravasation site should be infiltrated with 10–15 mL of saline solution containing 5–10 mg of phentolamine as soon as possible after the extravasation is noted [3, 7–9]. Using a fine hypodermic needle, the phentolamine solution should be infiltrated liberally throughout the extravasation area, which may be identified by its cold, hard, and pallid appearance [7]. When administered within 12 h of norepinephrine extravasation, phentolamine-induced sympathetic blockade can reduce tissue ischemia and prevent necrosis by causing local vasodilation, which can be visualized clinically as an immediate and conspicuous local hyperemic change [7]. Following the administration of phentolamine, the patient should be monitored for complications including hypotension, hyperemia, and pain from reperfusion of affected tissues [9].

The objective of this case report is to describe the successful use of phentolamine infusion for the management of clinically significant norepinephrine extravasation in a dog. To the authors' knowledge at the time of submission, there were no published reports of the clinical use of phentolamine for norepinephrine extravasation in veterinary medicine.

2 | CASE REPORT

An 8-year-old male neutered Labrador Retriever was presented to a veterinary teaching hospital for persistent anorexia, diarrhea, and weight loss 1 month after diagnosis and appropriate treatment for severe multi-systemic *Heterobilharzia americana* infection. The patient was diagnosed with a jejunoileocolic intussusception by abdominal ultrasound the day after presentation and subsequently underwent exploratory laparotomy with concurrent resection and anastomosis, along with tissue biopsies of the liver and jejunum. The patient had no prior history of ectoparasitism or dermatological disease.

Ninety minutes prior to anesthesia, the left antebrachium was circumferentially clipped of hair and aseptically prepared, and a 20-gauge PIVC[a] was placed in the cephalic vein. There were no obvious lesions on the limb at the time of PIVC placement, which was routine with successful placement on the second attempt. This PIVC was patent during anesthetic induction and was used as the primary PIVC to administer medications perioperatively. Immediately prior to anesthesia, a second PIVC was placed in the right dorsal pedal vein for backup IV access in the event the primary PIVC could not be used.

The patient was premedicated with fentanyl[b] (3 μg/kg, IV, once) and midazolam[c] (0.5 mg/kg, IV, once). Anesthesia was induced with propofol[d] (1.3 mg/kg, IV, titrated slowly to effect). He was intubated and mechanically ventilated with 100% oxygen. Anesthesia was maintained with sevoflurane[e] (0.8%–2% inhaled), fentanyl continuous rate infusion (CRI) (5–20 μg/kg/h, IV), and ketamine[f] CRI (1 mg/kg/h, IV). A lidocaine[g] CRI (3 mg/kg/h, IV) was provided intraoperatively for additional analgesia. Cefoxitin[h] (30 mg/kg, IV, every 90 min) was administered intraoperatively for antimicrobial prophylaxis. The dog also received a 5% canine lyophilized albumin transfusion[i] (10 g diluted in 200 mL of 0.9% NaCl and administered IV over 4 h) to treat hypoalbuminemia and provide perioperative colloidal support.

During surgery, the patient experienced systemic hypotension as measured via indirect oscillometric blood pressure; the lowest systolic and mean arterial blood pressures were 80 and 52 mm Hg, respectively. Hypotension was initially managed with intravenous crystalloid fluid boluses (lactated Ringer's solution[j] 5 mL/kg, IV, twice). Approximately 2 h after induction, a norepinephrine[k] CRI (0.3 μg/kg/min, IV; diluted to 100 μg/mL with 0.9% NaCl) was started for the treatment of persistent hypotension in the face of presumed adequate volume status. Over the next 2 h of surgery, the norepinephrine CRI was gradually titrated up from 0.3 to 1.5 μg/kg/min and appeared to be efficacious in maintaining blood pressure; mean arterial pressures remained between 60 and 80 mm Hg during this period.

Immediately following abdominal closure and removal of the sterile surgical drapes, the patient was noted to have new subcutaneous edema of the left antebrachium located proximal to the PIVC bandage. The patient was receiving five different CRIs through this PIVC at the time the edema was noted. The left cephalic PIVC was flushed with sterile saline and determined to be nonpatent. The fentanyl, lidocaine, and norepinephrine CRIs were relocated to the backup right dorsal pedal PIVC, and the lactated Ringer's solution and albumin CRIs were temporarily discontinued. The anesthetized patient was transported to radiology for placement of both a jugular CVC and an esophageal feeding tube. After CVC placement, the norepinephrine, fentanyl, and lidocaine CRIs were relocated to the CVC, and the lactated Ringer's solution and albumin CRIs were restarted through the right dorsal pedal PIVC. The patient was recovered uneventfully from anesthesia and returned to the ICU.

Following recovery from anesthesia, the left cephalic PIVC was removed, revealing a new lesion centered over the PIVC insertion site. The lesion was an approximately 2 × 3 cm, raised, thickened, apparently painful plaque that was initially only slightly darker in color than the surrounding skin, which had a generalized "blanched" appearance. There was moderate subcutaneous edema located circumferentially around the limb at the level of, and proximal to, the plaque. Neither aspiration of the PIVC nor irrigation of the subcutaneous space with sterile saline was performed prior to the removal of the PIVC. The affected limb was not elevated; however, a heat pack was applied to the extravasation site for approximately 10 min after PIVC removal.

Given the concern for perioperative extravasation of norepinephrine, Animal Poison Control[l] was consulted. The maximum possible volume of extravasated norepinephrine was determined to be 28 mL of 100 μg/mL norepinephrine solution yielding a total of 2.8 mg (or 89.2 μg/kg) of norepinephrine. Animal poison control had only one previous case report of subcutaneous norepinephrine extravasation in a dog in their database for which follow-up was not available. However, given the current recommendations from both the human literature and the black box warning on the norepinephrine drug label, phentolamine was recommended as the gold standard therapy [7]. Additionally, warm compresses and elevation of the affected limb were recommended in the acute period to promote vasodilation and systemic absorption [6].

Phentolamine infusion was performed within 11 h of the initiation of norepinephrine therapy and 5 h after the initial recognition of extravasation. Two 5-mg vials of phentolamine mesylate[m] were obtained from a local human hospital. Each 5-mg vial was reconstituted with 5 mL of sterile saline, producing 10 mL of a 1-mg/mL phentolamine mesylate solution. The entire 10 mL of the 1% phentolamine mesylate solution was aspirated into a single 12-mL syringe and administered subcutaneously, circumferentially around the plaque/left cephalic PIVC insertion site, using multiple new 25-gauge hypodermic needles[n]. Before small aliquots of phentolamine were instilled, the syringe was aspirated and lack of hemorrhage was confirmed. During the phentolamine infusion and for 30 min thereafter, the patient was monitored via oscillometric blood pressure every minute and remained normotensive with no clinical evidence of hemodynamic shock. Erythematous macules formed instantaneously at most, but not all, of the phentolamine injection sites. The macules were round, well-marginated, variably raised, variably sized (3–10 mm in diameter) hyperemic foci, some of which exuded a small bleb of hemorrhage upon removal of the needle from the skin (Figure 1). Additionally, the integument of the extravasation area had a generalized return of pink coloration.

Throughout the next 10 days of hospitalization, the extravasation site was closely monitored (Figure 2). At 12 h post-extravasation, the area previously noted as a dermal plaque became a distinct focus of necrosis; it was nearly black in color, thicker, more raised, and well marginated, with only a thin border of erythematous skin separating the plaque from the surrounding healthy epidermis (Figure 2A). At 36 h post-extravasation, the dermal plaque sloughed, revealing a shallow, nonpainful, mildly exudative dermal ulcer approximately 2 × 3 cm in size (Figure 2B). The ulcer was covered with a small Tegaderm bandage[o]. Initially, bandage changes were performed at least daily, but the wound was only minimally exudative, which soon allowed for bandage changes to be spaced out to every other day as the wound healed by secondary intention. At 7 days post-extravasation, the dermal ulcer had developed into a nonpainful, nonexudative crust (Figure 2C, left). At 9 days post-extravasation, the crust was nearly completely sloughed, revealing a healthy epidermis (Figure 2C, right). The erythematous macules and surrounding generalized hyperemia of the integument were completely resolved after approximately 24–36 h post-phentolamine infusion. The subcutaneous edema gradually resolved over 7 days post-extravasation.

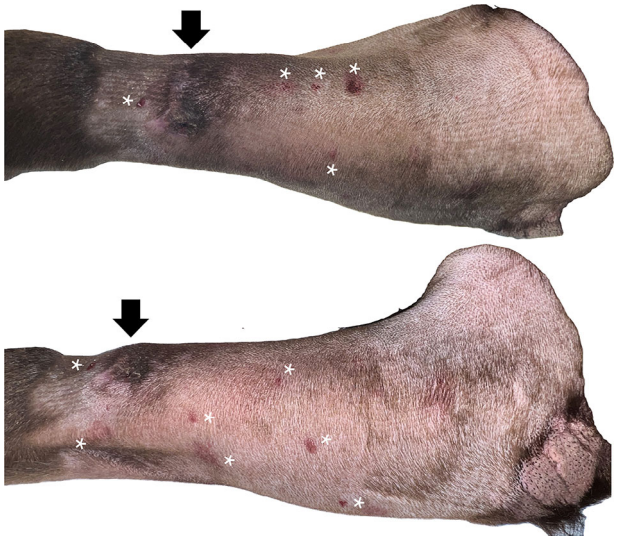

FIGURE 1 | Cranial (top) and lateral (bottom) aspects of the norepinephrine extravasation site at approximately 2 h after phentolamine infusion in a dog, demonstrating the plaque centered over the approximate peripheral intravenous catheter insertion site (arrow) and the erythematous macules that formed at each phentolamine injection site (*).

Histopathology results of the liver and jejunal biopsies revealed disseminated lymphoma, suspected to be malignant transformation secondary to schistosomiasis. At 10 days after surgery, the patient was euthanized due to continued clinical decline and poor prognosis for recovery. At the time of necropsy examination, only a small superficial crust was noted at the extravasation site.

3 | DISCUSSION

In veterinary medicine, peer-reviewed literature characterizing the occurrence, treatment, and outcome of vasopressor extravasation events is limited, and the incidence of vasopressor extravasation is currently unknown. In people, retrospective studies and systematic reviews have attempted to characterize the risk associated with peripheral and central administration of vasopressor solutions. One systematic review reported 325 events of vasopressor extravasation, 204 of which resulted in local tissue injury, including skin necrosis, tissue necrosis, and gangrene events [10]. Of these, 97.8% resulted from peripheral intravenous administration, while just 2.2% resulted from administration via CVCs, but the overall incidence of occurrence was not investigated [10]. A meta-analysis of 11 studies including 16,055 adult patients revealed a pooled incidence of adverse events associated with peripheral intravenous vasopressor administration of just 1.8%, while a meta-analysis of four studies including 388 children estimated this incidence at 3.3% [11]. Another systematic review identified seven cohort studies including 1362 adult patients in shock and documented 35 instances of vasopressor extravasation yielding an incidence rate of 3.4%, none of which resulted in tissue necrosis or limb ischemia [12]. Given the frequent use of vasopressor medications in veterinary anesthesia and critical care, increased reporting on the occurrence and outcome

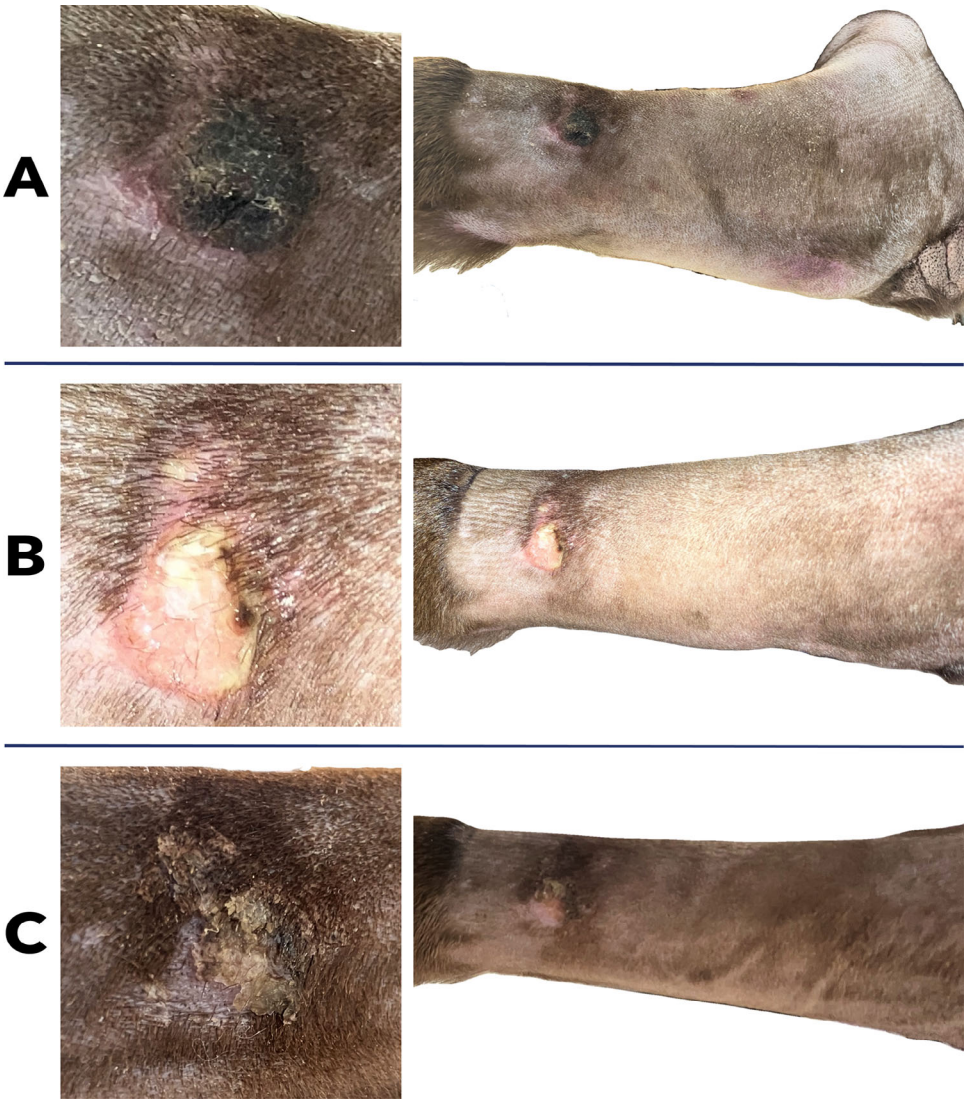

FIGURE 2 | Serial images of a norepinephrine extravasation site in a dog, with enlargement of the peripheral intravenous catheter insertion site at (A) approximately 12 h post-extravasation, (B) approximately 36 h post-extravasation, (C, left) approximately 7 days post-extravasation, and (C, right) approximately 9 days post-extravasation. In picture B, the ulcer bed contains granulation tissue undergoing epithelialization with a mild amount of serous discharge and fibrinous material.

of vasopressor extravasation events is warranted to determine clinical significance.

Until recently, peer-reviewed treatment recommendations for vasopressor extravasation in animals did not exist, so current human recommendations were translated to the canine patient [13]. Studies documenting the safety and efficacy of phentolamine administration in veterinary species are exceedingly rare. In one experimental study from 1957, dogs received subcutaneous infusions of diluted norepinephrine solution over a 50- to 70-min period, which "routinely" resulted in tissue necrosis and sloughing [14]. Some of these dogs received 10 mg of phentolamine infused subcutaneously within and around the margins of the site of subcutaneous norepinephrine administration, and the phentolamine infusion was found to be "dramatically effective" in preventing norepinephrine-induced tissue necrosis when "injected into the area of extravasation immediately or up to 12 h following extravasation" [14]. Furthermore, the phentolamine infusion had no effect on blood pressure [14]. In the current study, the coloration of the extravasation area rapidly improved from a "blanched" to a "pink" color following phentolamine infusion, which supports a positive response to therapy [6]. Furthermore, the authors hypothesize that the erythematous macules were a result of sudden, profound, focal vasodilation at the site of each phentolamine infusion, further supporting a positive response to therapy. These color changes to the integument are expected in people; however, they may be less apparent in canines due to species differences in anatomy (subcutaneous tissue, hair coat, etc.) and/or response to therapy.

Availability of phentolamine in the veterinary setting is unreliable given historical shortages, as well as the fact that it is not usually stocked in veterinary clinics [15]. A 2017 systematic review of alternative pharmacological treatment options for vasopressor extravasation in people proposed a treatment algorithm consisting of a combination of subcutaneous terbutaline (1 mg diluted

in 10 mL of saline, injected subcutaneously into the area of extravasation) and 2% nitroglycerin ointment (applied topically to cover the entire affected area) [15]. If there is inadequate improvement in signs of tissue ischemia, terbutaline can be repeated 15 min later. If improvement is seen but residual symptoms remain, nitroglycerin may be reapplied every 8 h until symptoms fully resolve [15]. The authors caution that the safety and efficacy of subcutaneous terbutaline administration have not been fully evaluated [15]. In contrast to terbutaline and nitroglycerin, the following alternative treatment options were found to have no beneficial effects: papaverine, procaine, hyaluronidase, and conivaptan [15].

Other recommended nonpharmacological therapies for vasopressor extravasation in people include aspirating the PIVC as soon as extravasation is identified, irrigating the subcutaneous space with sterile saline, and lastly removing the PIVC [3, 6, 9, 10]. Next, the affected limb should be elevated at a 45° angle, and the extravasation site should be warm-packed and closely monitored for the development of local tissue necrosis, which may require surgical debridement [3, 6, 9, 10]. Passive range of motion physiotherapy on the affected limb may also improve lymphatic and venous drainage of the extravasation site, thereby enhancing systemic absorption of the extravasated drug [13].

A recent veterinary case series documented the occurrence and management of vasopressor extravasation in three canine patients, all of which resulted from PIVC administration [13]. Associated complications were similar to those in the present study and included pain, areas of pallor, ecchymoses of the affected limb, and tissue necrosis [13]. All patients received a combination of nonpharmacological treatments (e.g., PIVC aspiration, warm compress, passive range of motion) and pharmacological treatments (i.e., tourniquet placement at the proximal and distal margins of extravasation site immediately before, and for 15 min following, subcutaneous terbutaline and topical nitroglycerin administration), which resulted in rapid erythema and reduced pain in the treated area [13]. Those authors outline a suggested treatment protocol for vasopressor extravasation in dogs, including nonpharmacological strategies, terbutaline and nitroglycerin dosing, and recommended monitoring [13]. In addition, at the time of submitting the current case report, a multicenter retrospective case series describing 14 cases of norepinephrine extravasation in dogs and cats was simultaneously in production for publication, describing complications secondary to extravasation, treatment strategies, and outcomes [16].

The patient in the current report developed extravasation site necrosis despite phentolamine infusion. However, the reader should not conclude that phentolamine infusion is an ineffective treatment for vasopressor extravasation in dogs as there were numerous complicating factors in this case. Phentolamine infusion is most effective if the treatment is started early (within 12 h of vasopressor extravasation) [6]. In the present study, the exact time of extravasation is unknown but may have occurred up to 11 h prior to phentolamine infusion. This patient also experienced concurrent extravasation of other potentially irritating medications (e.g., cephalosporins, canine lyophilized albumin). In addition, the PIVC was not aspirated back prior to removal, and the subcutaneous space was not irrigated with saline. Finally, a relatively high dose of norepinephrine was used in this case (up to 1.5 μg/kg/min) to achieve an appropriate blood pressure. The authors suggest that the patient in the present report may have benefitted from phentolamine administration by reduced severity of necrosis and more rapid recovery. The wound required only minimal care throughout the period of hospitalization; it declared itself early following the extravasation event, it was minimally exudative, and it rapidly healed by secondary intention. Further studies are needed to determine if phentolamine infusion is beneficial for veterinary patients experiencing vasopressor extravasation.

Given the paucity of information regarding the treatment of vasopressor extravasation in veterinary medicine, safe administration of vasopressors and prevention of extravasation should be a priority for all patients. In people, potential risk factors for local tissue injury secondary to vasopressor extravasation include vasopressor administration through distal PIVCs (i.e., distal to the antecubital or popliteal fossae), increased duration of vasopressor extravasation (i.e., >24 h), the degree of shock-induced tissue hypoperfusion in the distal extremities, higher concentration of vasopressor, and higher rate of vasopressor administration [9, 10, 17]. Therefore, vasopressors should be administered through CVCs when possible, especially if longer durations, higher rates, and higher concentrations are anticipated. However, when indicated in emergency situations and until a CVC is placed, short-term administration (<2 h) of vasopressors via proximal, well-placed PIVCs that are closely monitored is unlikely to result in local tissue injury [10, 12]. The need for vasopressors in veterinary patients may emerge rapidly in anesthesia and critical care situations. As demonstrated by the failures of this case, veterinary hospitals need to establish standard operating procedures for the administration of vasopressors and raise awareness about the risks and consequences of extravasation, as well as treatment protocols should extravasation occur.

Future study of this topic is necessary in veterinary medicine, including characterization of the prevalence and outcomes of vasopressor extravasation events in animals and treatment recommendations with alternative options. In addition, veterinary research devoted to the safe administration of vasopressors and prevention of extravasation is warranted.

Ethics Statement

All legal and ethical requirements have been met with regard to the humane treatment of animals described in the present study.

Conflicts of Interest

The authors declare no conflicts of interest.

Offprints

Offprints will not be available from the authors.

Endnotes

[a] Veterinary I.V. polyurethane catheter, Cardinal Health, Waukegan, IL.

[b] Fentanyl Citrate, Hospira Inc., Lake Forest, IL.

[c] Midazolam, Almaject, Inc., Morristown, NJ.

[d] Propofol Injectable Emulsion, Zoetis Inc., Kalamazoo, MI.

[e] Sevoflurane, Dechra Veterinary Products, Overland Park, KS.

[f] Ketamine hydrochloride, MWI, Boise, ID.

[g] Lidocaine 2%, MWI, Boise, ID.

[h] Cefoxitin, SAGENT Pharmaceuticals, Schaumburg, IL.

[i] Canine lyophilized albumin, Animal Blood Resources International, Stockbridge, MI.

[j] Lactated Ringer's Solution, Dechra Veterinary Products, Overland Park, KS.

[k] Norepinephrine Bitartrate Injection, Breckenridge Pharmaceutical Inc., Berlin, CT.

[l] ASPCA Animal Poison Control Center, Urbana, IL.

[m] Phentolamine mesylate, Hikma Pharmaceuticals USA Inc., Berkeley Heights, NJ.

[n] 25-gauge, hypodermic needle, BD, Franklin Lakes, NJ.

[o] Tegaderm Film, 3M, St. Paul, MN.

References

1. M. Singer, C. S. Deutschman, C. W. Seymour, et al., "The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)," *JAMA* 315, no. 8 (2016): 801–810, https://doi.org/10.1001/jama.2016.0287.

2. K. M. Murphy, M. Rishniw, and D. C. Silverstein, "Use of Vasopressors for Treatment of Vasodilatory Hypotension in Dogs and Cats by Diplomates of the American College of Veterinary Emergency and Critical Care," *Journal of Veterinary Emergency and Critical Care* 32, no. 6 (2022): 714–722, https://doi.org/10.1111/vec.13230.

3. S. S. Stefanos, T. H. Kiser, R. MacLaren, S. W. Mueller, and P. M. Reynolds, "Management of Noncytotoxic Extravasation Injuries: A Focused Update on Medications, Treatment Strategies, and Peripheral Administration of Vasopressors and Hypertonic Saline," *Pharmacotherapy* 43, no. 4 (2023): 321–337, https://doi.org/10.1002/phar.2794.

4. L. Evans, A. Rhodes, W. Alhazzani, et al., "Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021," *Intensive Care Medicine* 47, no. 11 (2021): 1181–1247, https://doi.org/10.1007/s00134-021-06506-y.

5. T. T. Nguyen, A. Surrey, B. Barmaan, et al., "Utilization and Extravasation of Peripheral Norepinephrine in the Emergency Department," *American Journal of Emergency Medicine* 39 (2021): 55–59, https://doi.org/10.1016/j.ajem.2020.01.014.

6. V. David, N. Christou, P. Etienne, et al., "Extravasation of Noncytotoxic Drugs," *Annals of Pharmacotherapy* 54, no. 8 (2020): 804–814, https://doi.org/10.1177/1060028020903406.

7. DailyMed, "Levophed(R) Norepinephrine Bitartrate Injection," HF Acquisition Co., LLC, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=788b6c64-1b6d-0058-e053-2a91aa0aa99c.

8. J. Ong and R. Van Gerpen, "Recommendations for Management of Noncytotoxic Vesicant Extravasations," *Journal of Infusion Nursing* 43, no. 6 (2020): 319–343, https://doi.org/10.1097/NAN.0000000000000392.

9. P. M. Reynolds, R. MacLaren, S. W. Mueller, D. N. Fish, and T. H. Kiser, "Management of Extravasation Injuries: A Focused Evaluation of Noncytotoxic Medications," *Pharmacotherapy* 34, no. 6 (2014): 617–632, https://doi.org/10.1002/phar.1396.

10. O. M. Loubani and R. S. Green, "A Systematic Review of Extravasation and Local Tissue Injury From Administration of Vasopressors Through Peripheral Intravenous Catheters and Central Venous Catheters," *Journal of Critical Care* 30, no. 3 (2015): 653.e9–653.e17, https://doi.org/10.1016/j.jcrc.2015.01.014.

11. V. S. Owen, B. K. Rosgen, S. J. Cherak, et al., "Adverse Events Associated With Administration of Vasopressor Medications Through a Peripheral Intravenous Catheter: A Systematic Review and Meta-Analysis," *Critical Care* 25, no. 1 (2021): 146, https://doi.org/10.1186/s13054-021-03553-1.

12. D. H. Tian, C. Smyth, G. Keijzers, et al., "Safety of Peripheral Administration of Vasopressor Medications: A Systematic Review," *Emergency Medicine Australasia* 32, no. 2 (2020): 220–227, https://doi.org/10.1111/1742-6723.13406.

13. C. N. Lathroum, H. L. Angulo Bracho, K. M. Alessandrino, and J. M. Walker, "The Use of Injectable Subcutaneous Terbutaline and Topical Nitroglycerin Ointment in the Treatment of Peripheral Vasopressor Extravasation in 3 Dogs," *Journal of Veterinary Emergency and Critical Care* 34, no. 4 (2024): 393–398, https://doi.org/10.1111/vec.13393.

14. J. Y. Berben, M. F. Bryant, and J. M. Howard, "Etiology and Prevention of Sloughs Produced by L-Norepinephrine (Levophed)," *Annals of Surgery* 146, no. 6 (1957): 1016–1020, https://doi.org/10.1097/00000658-195712000-00019.

15. M. Plum and O. Moukhachen, "Alternative Pharmacological Management of Vasopressor Extravasation in the Absence of Phentolamine," *Pharmacy and Therapeutics* 42, no. 9 (2017): 581–592.

16. M. P. Vasquez, M. Daly, C. J. Boyd, et al., "Multicenter Retrospective Evaluation of Norepinephrine Extravasation in Dogs and Cats (2015-2021): 14 Cases," *Journal of Veterinary Emergency and Critical Care* 35 (2025): 73–80.

17. B. Nickel, "Peripheral Intravenous Administration of High-Risk Infusions in Critical Care: A Risk-Benefit Analysis," *Critical Care Nurse* 39, no. 6 (2019): 16–28, https://doi.org/10.4037/ccn2019443.