Journal of Medical Toxicology
https://doi.org/10.1007/s13181-025-01089-2

ORIGINAL ARTICLE

Efficacy of Treating Nifedipine-Induced Shock with Hydroxocobalamin in a Swine Model

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Received: 28 March 2025 / Revised: 6 July 2025 / Accepted: 16 July 2025

Abstract

Introduction Calcium channel antagonists contribute to many overdose related deaths each year and treatment options are limited. Hydroxocobalamin has shown promise in reversal of multiple shock states, and we evaluated its use in the treatment of nifedipine-induced shock in a swine model.

Methods Twenty-two swine (39 to 50 kg) were anesthetized, instrumented, and acclimatized. Toxicity was induced by administering a nifedipine infusion at 0.0266 mg/kg/min. Once the toxic end point, defined as a 20% decrease from the initial mean arterial pressure, was reached, all animals received a 20 mL/kg bolus of saline and either 60 mL of saline (NP group) or 150 mg/kg of hydroxocobalamin dissolved in 60 mL of saline (NP + HX group). Hemodynamics were analyzed and compared between the NP and NP + HX groups over time using linear mixed models with Bonferroni correction.

Results Modeling of the hemodynamic data demonstrated an increase in both systolic blood pressure and change in MAP from the nadir. Mean arterial pressure (MAP) and diastolic blood pressure were increased ($p < 0.01$) in the NP + HX group at multiple time points. There were no differences detected in the time-to-death between groups.

Conclusion Improvements in hemodynamics were noted in the group treated with hydroxocobalamin, but there was no evidence for improvement in mortality. Given this, hydroxocobalamin may serve a role in bridging patients to high dose insulin, vasopressors, extracorporeal membrane oxygenation, or transfer to a higher level of care.

Keywords Hydroxocobalamin · Calcium channel antagonist · Nifedipine · Swine · Toxicity

Introduction

Between 2017 and 2022, approximately 5% of all exposure related fatalities reported annually to the National Poison Data System have been attributed to calcium channel antagonists [1–6]. These medications remain deadly in overdose despite advances in critical care. While high dose insulin therapy has proven effective in treating patients with intractable hypotension related to calcium channel antagonist and beta-blocker overdoses, physicians remain reluctant to implement this treatment strategy out of concern for inducing hypoglycemia, lack of technical expertise, and hypokalemia [7–11].

Nifedipine, a dihydropyridine calcium channel antagonist, causes vasodilation through the inhibition of L-type calcium channels in smooth muscle cells, thereby decreasing the overall amount of intracellular calcium, which is required for vasoconstriction. Nifedipine may also induce vasodilation through the nitric oxide (NO) pathway [12, 13]. Several studies have demonstrated that NO is an important chemical mediator of vasoplegic shock [14–19]. Production of NO is increased during periods of cellular stress and leads to blood vessel dilation and hypotension [16–18].

Hydroxocobalamin inhibits nitric oxide synthase and scavenges nitric oxide (NO), and this activity has been linked to increases in mean arterial pressure (MAP) [20–23]. Hydroxocobalamin is currently approved for treating cyanide toxicity and has an established safety profile and known "adverse effect" of increasing blood pressure [24].

Supervising Editor: Michael Levine, MD

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Published online: 04 August 2025

This effect is noted in healthy humans and humans treated for cyanide toxicity [25–28]. Human studies have demonstrated the successful use of hydroxocobalamin in treating vasoplegic shock during cardiac bypass [29–31]. There is also large animal data demonstrating improved hemodynamics and mortality following hydroxocobalamin administration in swine models of cyanide toxicity, sepsis, and hemorrhagic shock [32–38].

Given hydroxocobalamin's ability to antagonize NO activity, as well as its demonstrated ability to increase MAP in healthy volunteers and improve hemodynamics in other shock states, we hypothesize hydroxocobalamin may be an effective therapy for toxin related hypotension. In this study, we examined the effect of hydroxocobalamin treatment on the hemodynamics and mortality of swine with severe nifedipine toxicity.

Methods

Our Institutional Animal Care and Use Committee approved this research. The care and handling of animals was in accordance with guidelines of the American Association for Accreditation of Laboratory Animal Care. Yorkshire pigs, weighing 36 to 50 kg, were acquired and acclimated for a minimum of seven days. Twelve hours prior to the study, animals were fasted but had ad libitum water access. Animals were sedated with intramuscular tiletamine and zolazepam (200 mg), atropine (2 mg), xylazine (75 mg), weighed and then intubated. Weights obtained on the day of the experiment were used to calculate all additional drug and fluid doses. Intramuscular buprenorphine (1 mg) was given, peripheral intravenous (IV) access obtained, and animals were placed on the ventilator. Electrocardiogram electrodes were attached for continuous cardiac monitoring. Warming blankets were used to maintain baseline temperature. A bolus dose of α-chloralose (60 mg/kg) was given peripherally and animals started on an α-chloralose infusion of 25 mg/kg/hour. Anesthesia was maintained with the α-chloralose infusion, as needed bolus doses of α-chloralose, and as needed bolus doses of diazepam (0.5–1 mg/kg). Animals were started on IV maintenance sodium chloride 0.9% at 4 mL/kg/hour for the duration of the study.

Instrumentation

Carotid artery and internal jugular vein access was obtained via mid-lateral cut down of the neck, and both an arterial line and multiport venous line were placed. This allowed for continuous systolic, diastolic, and mean arterial pressure monitoring. A femoral cutdown was also performed with placement of a central venous catheter for drug delivery and arterial line for blood sampling.

Monitoring

Baseline measurements were collected on each animal following the completion of instrumentation. Measurements included systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, central venous pressure, end-tidal CO2 (ETCO2), arterial blood gas, base excess, lactate, glucose, creatinine, and mortality. Animals were monitored for a minimum of 30 min prior to the initiation of the experimental protocol to ensure stabilization.

Nifedipine

A solution of 4.95 mg/mL nifedipine was prepared daily using 300 mg of nifedipine powder dissolved at room temperature in 36 mL ethanol, 15 mL 400 polyethylene glycol (national formulary grade), and 10 mL 0.9% sodium chloride. Due to the light sensitive nature of nifedipine, it was prepared in a dark room with all containers, syringes, and IV tubing covered to avoid contact with light [9]. Previous literature has documented no effect of the diluents alone on hemodynamics of this animal model over a two-hour period [9]. Preliminary dose response curves were performed using eight animals to identify ideal dosing of nifedipine with the goal of achieving > 50% mortality between hour three and four of the protocol. The optimal dose of nifedipine was identified as 0.0266 mg/kg/min (Fig. 1A).

Hydroxocobalamin

Once the dose of nifedipine was identified, preliminary dose response curves using four animals were performed to identify dosing of hydroxocobalamin that decreased mortality in swine receiving 0.0266 mg/kg/min of a nifedipine infusion (Fig. 1B). Doses of 150 mg/kg and 300 mg/kg were tested. To prepare the solution and control for volume delivered, each 150 mg/kg dose of hydroxocobalamin was dissolved in 60 mL of sterile saline and 120 mL of sterile saline was used to dissolve hydroxocobalamin doses of 300 mg/kg. The optimal dose of hydroxocobalamin was identified as 150 mg/kg (Fig. 1B).

Experimental Protocol

Due to the known side effects of hydroxocobalamin such as skin discoloration, secretion discoloration, and altered reading of peripheral oxygen monitors, blinding was not pursued. Animals were placed in one of three groups on the day of the experiment: surgical control (SC) ($n=4$),

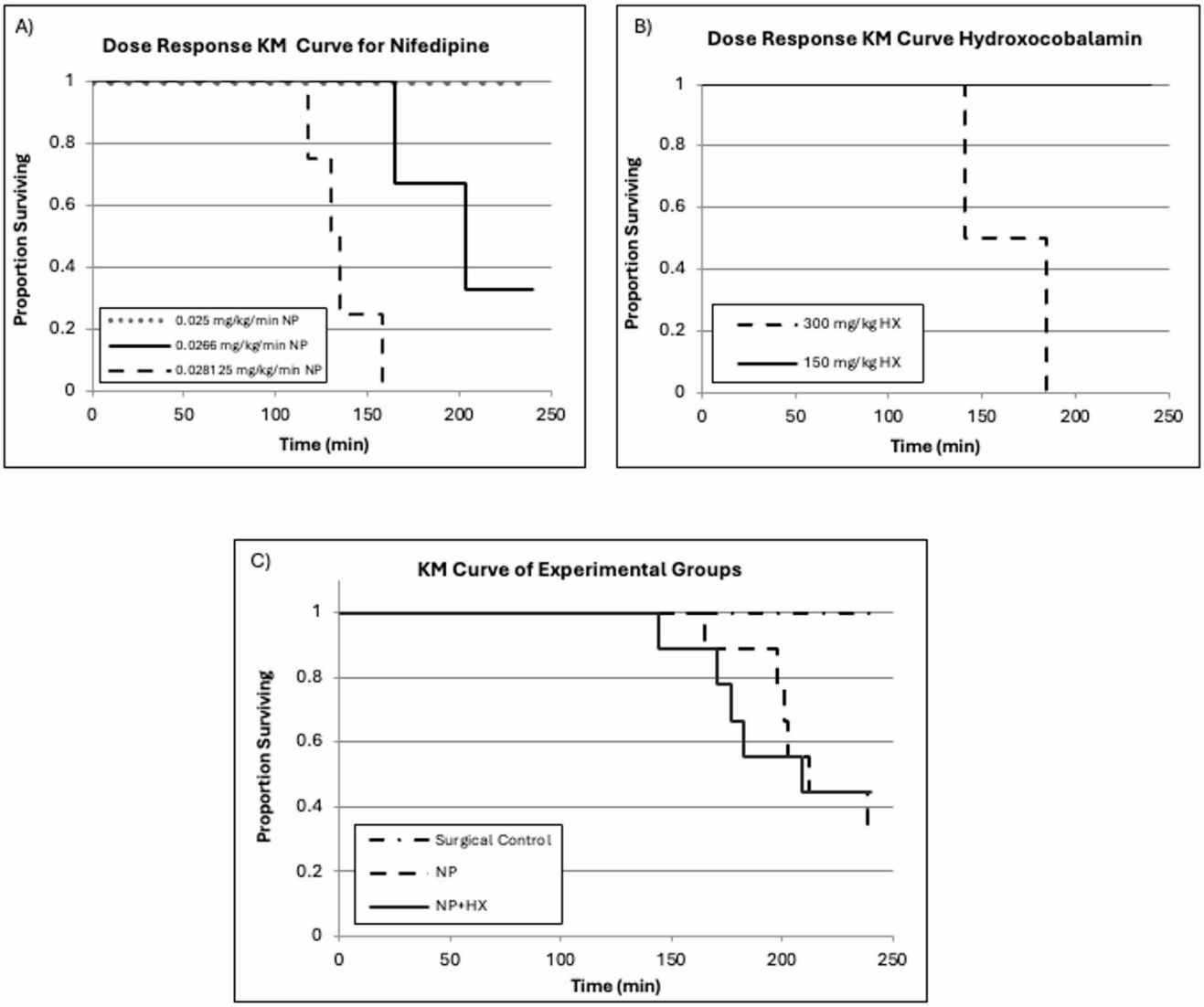

Fig. 1 (**A**) Kaplan-Meier (KM) curve demonstrating preliminary dose response study survival data at different doses of nifedipine (NP) with the ideal dose capable of causing > 50% mortality between hour three and four of the protocol. (**B**) Kaplan-Meier curve demonstrating preliminary dose response study survival data at 150 mg/kg versus 300 mg/kg hydroxocobalamin (HX) once toxicity achieved with a nifedipine infusion of 0.0266 mg/kg/min. (**C**) Kaplan-Meier curve of survival data for experimental protocol with surgical control, nifedipine + saline (0.0266 mg/kg/min; NP), and nifedipine + hydroxocobalamin (150 mg/kg; NP + HX)

nifedipine + saline (NP) ($n = 9$), nifedipine + hydroxocobalamin (NP + HX) ($n = 9$). Following the minimum 30-minute stabilization period, the nifedipine infusion (0.0266 mg/kg/min) was started and continued for four hours to simulate continued drug absorption in overdose in the NP and NP + HX groups. Once animals reached the point of toxicity, defined as a 20% decrease in MAP, a 20 mL/kg bolus of saline was infused over three to four minutes to simulate standard initial resuscitation treatment. The NP group then received 60 mL of saline and the NP + HX group then received 60 mL of hydroxocobalamin (150 mg/kg) over four minutes. Animals in the SC group received an appropriate volume of saline as an infusion to mimic nifedipine dosing throughout the four-hour protocol, as well as 60 mL of saline to simulate hydroxocobalamin dosing. Arterial blood was obtained for laboratory studies every 30 min. Point of care testing was performed using Abbott iStat machine (Abbott Laboratories, Abbott Park, IL). Vital signs were documented in 10-minute intervals. The total experimental protocol lasted four hours or until time of death, which ever occurred first. Any animal living at the end of the protocol was euthanized with a pentobarbital sodium and phenytoin sodium solution (Euthasol®).

Outcome Measures

The primary outcome of this study was to evaluate mortality in animals with nifedipine-induced shock treated with hydroxocobalamin. The secondary outcome was to assess the impact on physiologic parameters in response to treatment with hydroxocobalamin versus saline this model of nifedipine-induced shock. This included evaluating for changes in hemodynamics (HR, MAP, SBP, DBP), as well as improvements in pH, lactate, base excess, bicarbonate, glucose, and creatinine.

Statistical Analysis

Descriptive statistics using a two-sample t-test were used to compare average weights, total α-chloralose received, MAP characteristics and time to death of animals in each group. Hemodynamic measures (HR, MAP, SBP, DBP) were compared between animals in the NP and NP+HX groups over time using linear mixed models with random animal and slope effects and fixed effects for group, linear time, quadratic time, and the corresponding interaction terms. As this was a randomized study, we did not adjust for variables. Quadratic modeling was used to fit the hemodynamic measures as the measures were not linear over time. The interaction effects tested for differences in the linear and curvature patterns over time between groups. Random effects were fit to account for repeated measures within animal and variability in animal-specific slopes. Since hemodynamic measures were censored after death, imputation for the measures were carried assuming missing not at random (MNAR). Simple analyses on observed data from surviving animals could lead to biased results if time to death varied between groups. Predicted means of the outcomes (SBP, DBP, MAP, change in MAP from nadir) were plotted to examine the relationship of the hemodynamic measures by group over time. Least square means of hemodynamic measures were compared at specific time points with Bonferroni correction due to multiple testing. All analyses used a 2-sided test with a significance level of 0.05 except for time specific testing. All analyses were conducted using the SAS Enterprise Guide software version 6.1 (SAS Institute Inc, Cary, NC).

Results

During the protocol, there were no clinical differences in the mean amount of α-chloralose used, initial MAP, time to toxicity, how much the MAP dropped at the point of toxicity, or the lowest MAP when comparing the NP and NP+HX groups (Table 1). No basal differences were identified in animals prior to initiating the experimental protocol in HR, MAP, SBP, DBP (Table 2). Laboratory studies including pH, lactate, base excess, bicarbonate, glucose, and creatinine were also analyzed at multiple time points between the NP and NP+HX groups with no differences noted between the groups (see Supplementary Material). The mean time to death following the initiation of toxicity in the NP group was 215±25 min. Three animals survived in the NP group. The mean time to death following initiation of toxicity in the NP+HX group was 205±35 min, and four animals survived (Fig. 1C). There was no difference detected in time to death between the NP and NP+HX groups ($p=0.97$).

Missing not at random adjusted modeling of the hemodynamic measures demonstrated an increase in SBP in the NP+HX group ($p=0.02$) after treatment with hydroxocobalamin (Fig. 2A). No differences were detected in DBP ($p=0.32$) or MAP ($p=0.067$) when comparing the response to treatment between the NP+HX and NP models (Fig. 2B & C). However, when comparing NP+HX and NP models of the change in MAP from the nadir following treatment, there was an increase in the NP+HX group ($p=0.015$) (Fig. 2D). Once the animals began to decline, the rate of decrease was faster in the NP+HX group compared to the NP group in modeling of SBP ($p<0.0001$), DBP ($p<0.040$), MAP ($p=0.0018$), and change in MAP from nadir ($p<0.0001$) (Fig. 2A-D). When comparing hemodynamics at specific time points, MAP was higher ($p\leq0.01$) in the NP+HX group at 30, 60, and 90 min. Diastolic blood

Table 1 Comparison of average weights, total α-chloralose received, MAP characteristics, time to toxicity, and time to death of animals in each group. NP=nifedipine+saline; NP+HX=nifedipine+hydroxocobalamin; map=mean arterial pressure. Values reported as mean ± standard deviation. No significant differences identified between groups

	Surgical Control ($n=4$)	NP ($n=9$)	NP+HX ($n=9$)
Weight (kg)	43±2	46±3	44±3
Total α-chloralose given (mL)	578±193	588±122	608±135
Time to toxicity (min)	---	5±2	5±1
MAP at point of toxicity	---	82±10	83±6
Decrease in MAP at point of toxicity (%)	---	22±3	22±2
MAP at nadir	---	43±5	44±5
Decrease in MAP at nadir (%)	---	59±3	57±6
Time to death (min)	---	215±25	205±35

Table 2 Hemodynamic measures analyzed for each group. Values reported as mean ± standard deviation. NP = nifedipine + saline; NP + HX = nifedipine + hydroxocobalamin; map = mean arterial pressure; Δ map = change in MAP from nadir; sbp = systolic blood pressure; dbp = diastolic blood pressure; hr = heart rate. * = $p < 0.01$

Hemodynamic Measures												
	Basal		30 min		60 min		90 min		120 min		180 min	
	NP ($n=9$)	NP + HX ($n=9$)	NP ($n=9$)	NP + HX ($n=9$)	NP ($n=9$)	NP + HX ($n=9$)	NP ($n=9$)	NP + HX ($n=9$)	NP ($n=9$)	NP + HX ($n=9$)	NP ($n=8$)	NP + HX ($n=6$)
MAP	104±15	105±8	50±8	**63±15***	55±7	**72±15***	59±10	**79±14***	58±16	77±20	49±14	85±10
Δ MAP	NA	NA	10±4	20±11	14±6	29±12	14±12	36±12	14±16	28±24	1±17	34±14
SBP (mmHg)	133±10	135±7	78±23	98±24	90±23	118±22	103±35	133±34	100±137	134±52	83±23	152±30
DBP (mmHg)	81±10	84±7	36±4	**47±12***	38±3	**50±11***	39±3	**53±12***	38±8	**51±12***	34±10	50±10
HR (bpm)	80±12	73±10	129±22	133±9	154±18	155±17	172±24	169±14	180±25	177±17	166±38	195±10

pressure was also higher ($p \leq 0.01$) in the NP + HX group at 30, 60, 90, and 120 min (Table 1).

Discussion

We developed a model of nifedipine toxicity in swine with highly reproducible endpoints. We believe this is the first swine model evaluating the utility of hydroxocobalamin as a treatment for calcium channel antagonist toxicity. In this study, both SBP and the change in MAP from the lowest documented MAP (nadir) increased significantly following bolus infusion of hydroxocobalamin once the animals met the pre-defined level of toxicity. These effects were not sustained for the entire protocol, but this is not surprising given in multiple studies of healthy human volunteers where increases in MAP and blood pressure only lasted 20 min to four hours following hydroxocobalamin infusion [25–27]. Based on studies by Uhl et al., these changes are likely related to the nitric oxide scavenging nature of hydroxocobalamin itself and not other cobalamin derivatives in the plasma [26]. Uhl's research also suggests hydroxocobalamin's effects may be short lived as hydroxocobalamin is a reactive cobalamin derivative that quickly forms other cobalamin derivatives in the plasma [26]. This could also explain the faster rate of decrease in SBP, DBP, MAP, and change in MAP from nadir, as the effects of hydroxocobalamin abated and the animals' condition declined. This theory is further supported by several cases reported in the literature where patients received "extended duration infusions" of 5 g doses of hydroxocobalamin over an average of six hours [39, 40]. Based on this and the transient improvement seen in hemodynamics in the group treated with hydroxocobalamin, an alternative dosing strategy is likely needed in treating toxin-induced vasoplegia, and a continuous infusion over a longer period of time may prove more beneficial than giving a second dose or a bolus followed by infusion.

While hemodynamics improved in the group treated with hydroxocobalamin, overall mortality was not affected in our study. It is difficult to compare this result to other swine studies where mortality improved following hydroxocobalamin administration, given the different nature of the toxins involved, as well as the different experimental endpoints. For example, the duration of our protocol was 240 min compared to published swine models of cyanide toxicity where hydroxocobalamin improved mortality, which have 60 min endpoints [32–34, 41, 42].

Given the improvements in SBP and change in MAP, we believe our data supports the use of hydroxocobalamin as an adjunct to other therapies and may serve as a bridge to more definitive care options such as extracorporeal membrane oxygenation (ECMO) [43]. Hydroxocobalamin may

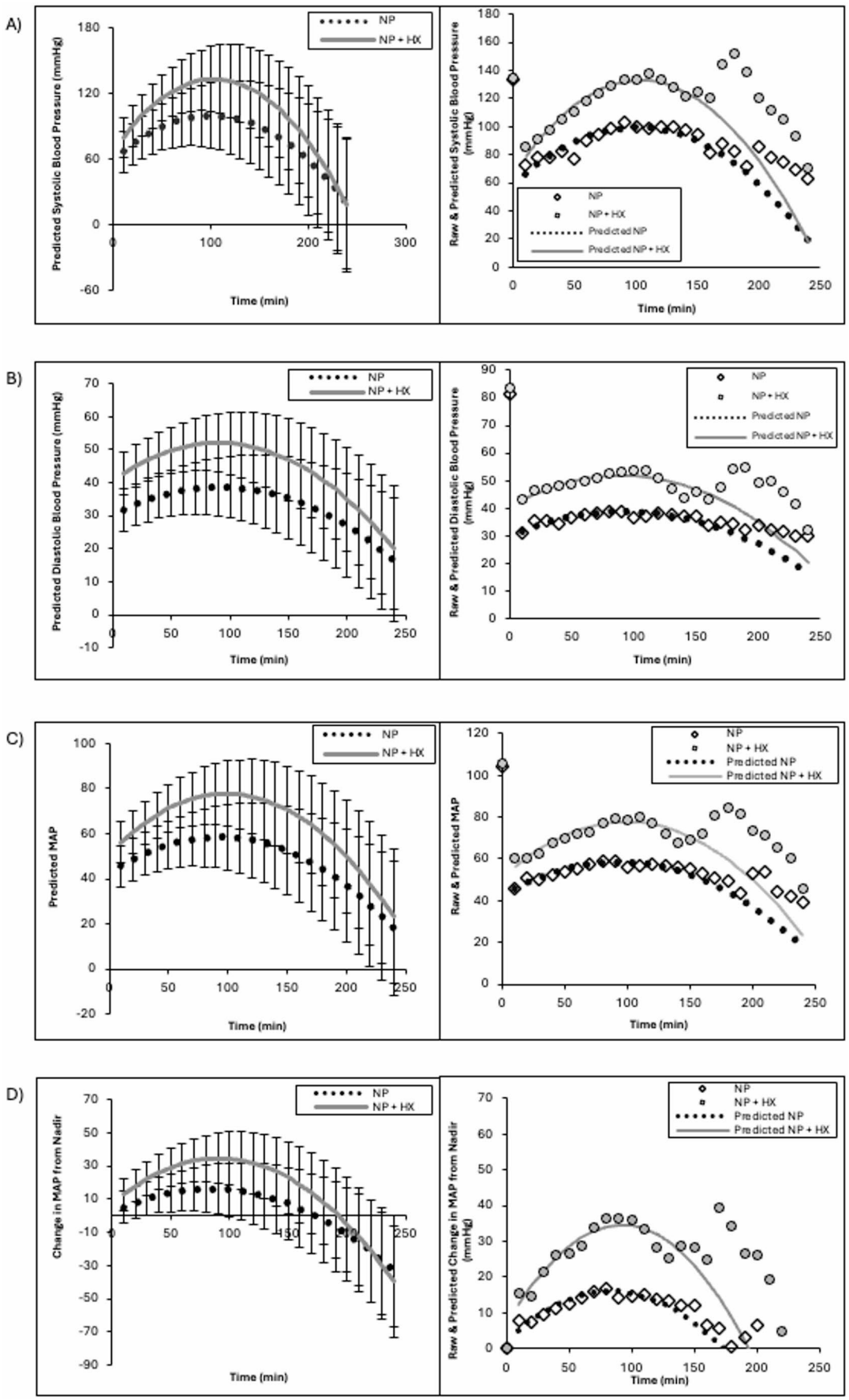
A)
Predicted Systolic Blood Pressure (mmHg)
Time (min)
NP
NP + HX
Raw & Predicted Systolic Blood Pressure (mmHg)
Predicted NP
Predicted NP + HX
B)
Predicted Diastolic Blood Pressure (mmHg)
Raw & Predicted Diastolic Blood Pressure (mmHg)
C)
Predicted MAP
Raw & Predicted MAP
D)
Change in MAP from Nadir
Raw & Predicted Change in MAP from Nadir

Fig. 2 (**A**) Predicted modeling of systolic blood pressure of nifedipine+saline (NP) and nifedipine+hydroxocobalamin (NP+HX) in panel on left with raw data superimposed on graph of predicted data on right. (**B**) Predicted modeling of diastolic blood pressure of NP and NP+HX treatment groups in panel on left with raw data superimposed on graph of predicted data on right. (**C**) Predicted modeling of mean arterial pressure (MAP) of NP and NP+HX groups in panel on left with raw data superimposed on graph of predicted data on right. (**D**) Predicted modeling of the change in MAP from the nadir of NP and NP+HX groups in panel on left with raw data superimposed on graph of predicted data on right

be beneficial in the scenarios where a patient arrives with or develops critical vasoplegia while titrating insulin or vasopressor infusions. Additionally, while high dose insulin therapy is considered the treatment of choice for calcium channel antagonist overdoses, some providers are hesitant initiating and titrating insulin infusions to recommended doses, and hydroxocobalamin may provide some benefit in the short term as a treatment adjunct or while patients await transfer to a tertiary care facility.

There were multiple limitations in this study. This was a swine model of toxicity, and while swine are an ideal model for multiple types of shock, we recognize results do not always directly translate to the bedside care of patients. We must also consider that, despite previous experiments using similarly defined markers of toxicity [9, 44] and similar doses of nifedipine [44], the animals were too sick to survive at the point we initiated resuscitation. In this study, our goal was to identify a treatment for refractory hypotension and overdoses of calcium channel antagonists are known to cause severe/intractable hypotension. Nifedipine was chosen as other calcium channel antagonist drugs such as diltiazem (benzothiazepine class) and verapamil (phenylalkylamine class) have significant cardiac conduction and myocardial contractile effects in addition to effects on peripheral vascular activity. We intentionally did not use alternative calcium channel antagonists due to concerns these effects would overshadow/preclude the potential experimental treatment effect on blood pressure but must consider the effects of hydroxocobalamin noted in this study may differ in other types of calcium channel antagonist overdose. While the dose of hydroxocobalamin used in this study is higher than a typical initial dose in humans, it was chosen based on previous work using hydroxocobalamin in swine models of shock [33, 34, 38]. Other considerations regarding the dose of hydroxocobalamin used include using an insufficient dose of hydroxocobalamin or more likely an ineffective dosing strategy, and broader preliminary dose finding studies should be evaluated in the future. Additionally, the use of the Bonferroni correction in our analysis of hemodynamics at given time points may have been too conservative.

Conclusion

Hydroxocobalamin did not improve mortality in this model. Significant but transient improvements in hemodynamics were noted with analysis of modeled hemodynamic data. This suggests that hydroxocobalamin may serve a role in bridging patients to optimal doses of standard therapies like high dose insulin and vasopressors, as well as alternative therapies like ECMO, or transfer to a higher level of care. Further investigation of hydroxocobalamin as a treatment for nifedipine and other calcium channel antagonist toxicity is warranted. Specifically needed are studies evaluating the clinical significance of hemodynamic improvements noted in this study, alternative hydroxocobalamin dosing strategies to include the evaluation of infusion versus bolus dosing, and comparison of the effects of hydroxocobalamin against standard vasopressors and high dose insulin.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13181-025-01089-2.

Acknowledgements The investigators wish to thank several parties for their support of this research: the Carolinas Medical Center Department of Emergency Medicine's John A. Marx, MD Scholarship Fund, as well as the American College of Medical Toxicology and Medical Toxicology Foundation's Innovative Research Grant; Vik Bebarta and Dave Tanen for support and guidance with hydroxocobalamin dosing; and the Comparative Medicine Core Facility staff for their assistance and support of this project.

Funding Funding for this study was provided by the Medical Toxicology Foundation Innovative Teaching and Research Grant and the John A. Marx, MD Scholarship Fund.

Declarations

Previous Presentation This research was presented at the American College of Medical Toxicology Annual Scientific Meeting in Huntington Beach, California, 2016.

Conflict of Interest None to disclose.

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