

ORIGINAL CONTRIBUTION

Intraosseous Versus Intravenous Infusion of Hydroxocobalamin for the Treatment Of Acute Severe Cyanide Toxicity in a Swine Model

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Abstract

Objectives: Easily administrated cyanide antidotes are needed for first responders, military troops, and emergency department staff after cyanide exposure in mass casualty incidents or due to smoke inhalation during fires involving many victims. Hydroxocobalamin has proven to be an effective antidote, but cannot be given intramuscularly because the volume of diluent needed is too large. Thus, intraosseous (IO) infusion may be an alternative, as it is simple and has been recommended for the administration of other resuscitation drugs. The primary objective of this study was to compare the efficacy of IO delivery of hydroxocobalamin to intravenous (IV) injection for the management of acute cyanide toxicity in a well-described porcine model.

Methods: Twenty-four swine (45 to 55 kg) were anesthetized, intubated, and instrumented with continuous mean arterial pressure (MAP) and cardiac output monitoring. Cyanide was continuously infused until severe hypotension (50% of baseline MAP), followed by IO or IV hydroxocobalamin treatment. Animals were randomly assigned to receive IV (150 mg/kg) or IO (150 mg/kg) hydroxocobalamin and monitored for 60 minutes after start of antidotal infusion. The primary outcome measure was the change in MAP after antidotal treatment from onset of hypotension (time zero) to 60 minutes. A sample size of 12 animals per group was determined by group size analysis based on power of 80% to detect a one standard deviation of the mean MAP between the groups with an alpha of 0.05. Whole blood cyanide, lactate, pH, nitrotyrosine (nitric oxide marker) levels, cerebral and renal near infrared spectrometry (NIRS) oxygenation, and inflammatory markers were also measured. Repeated-measures analysis of variance was used to determine statistically significant changes between groups over time.

Results: At baseline and at the point of hypotension, physiologic parameters were similar between groups. At the conclusion of the study, 10 out of 12 animals in the IV group and 10 out of 12 in IO group survived ($p = 1.0$). Both groups demonstrated a similar return to baseline MAP ($p = 0.997$). Cardiac output, oxygen saturation, and systemic vascular resistance were also found to be similar between groups ($p > 0.4$), and no difference was detected between bicarbonate, pH, and lactate levels ($p > 0.8$). Cyanide levels were undetectable after the hydroxocobalamin infusion throughout the study in both groups ($p = 1.0$). Cerebral and renal NIRS oxygenation decreased in parallel to MAP during cyanide infusion and increased after antidote infusion in both groups. Serum nitrotyrosine increased during cyanide infusion in all animals and then decreased in both study arms after hydroxocobalamin infusion ($p > 0.5$). Serum cytokines increased starting at cyanide infusion and no difference was detected between groups (tumor necrosis factor- α , interleukin [IL]-1 β , IL-6, and IL-10).

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Conclusions: The authors found no difference in the efficacy of IV versus IO hydroxocobalamin in the treatment of severe cyanide toxicity in a validated porcine model.

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Cyanide exposure is common, and acute severe cyanide toxicity can cause hypotension and cardiac arrest in 50% of cyanide-exposed patients.^{1,2} In addition, smoke inhalation has produced toxic cyanide levels in over 30% of patients who died after smoke inhalation.^{2–4}

Hydroxocobalamin is approved by the U.S. Food and Drug Administration for the treatment of cyanide toxicity. We have previously reported on the efficacy of intravenously (IV) administered hydroxocobalamin for cyanide-induced shock and cardiac arrest in animals.^{5–7} However, in a mass casualty incident or after a structure fire involving many victims, rapid administration by non-IV routes are needed.⁸ IV administration requires skilled personnel and fatigable dexterity. It is difficult to perform it in the dark, and conditions such as shock or wearing personal protective equipment may warrant alternative routes to IV delivery.^{8,9} Federal research agencies have also requested non-IV administration of chemical countermeasures, with particular emphasis on the intramuscular route.¹⁰ Hydroxocobalamin cannot be administered intramuscularly because of the large volume of fluid required for administration.^{6,11}

Intraosseous (IO) infusion, a well-established method of medication and fluid delivery, has been advocated as a reliable substitute for resuscitation for mass casualty incidents and first responders.¹² It can be performed with minimal skill, has few adverse effects, and has an infusion time similar to central venous access.^{13–15} It has also been studied for hydroxocobalamin administration and has a similar pharmacokinetic profile and feasibility to IV infusion in large animal models.^{4,11} However, to the best of our knowledge no published report has evaluated the efficacy of IO infusion of hydroxocobalamin in an acute cyanide toxicity model or directly compared it to IV hydroxocobalamin. The objective of this study was

to compare the efficacy of IO versus IV hydroxocobalamin in a porcine model of acute severe cyanide toxicity.

METHODS

Study Design

We conducted a randomized comparative laboratory investigation. The local Institutional Animal Care and Use Committee approved the protocol. All animal procedures complied with the regulations and guidelines of the Animal Welfare Act, the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and the American Association for Accreditation of Laboratory Animal Care. The housing of animals and the performance of the study took place in the animal care facility at our institution. The study was funded by the U.S. Air Force Office of the Surgeon General.

Animal Subjects

Yorkshire swine (*Sus scrofa*; $N = 24$, weighing 45 to 55 kg) of both sexes were premedicated with intramuscular ketamine 10 mg/kg. General anesthesia was induced with isoflurane via nose cone. Following endotracheal intubation, the animals were mechanically ventilated with a volume-limited, time-cycled ventilator (Dräger-Siemens, Fabius GS anesthesia machine) and maintained with inhaled isoflurane (1% to 3%) and oxygen (fraction of inspired oxygen [FiO₂] of 0.4 to 0.45). The tidal volume was initially set to 8 to 10 mL/kg and respiratory rate to 12 breaths/min. The minute ventilation was adjusted to maintain an end-tidal CO₂ value between 38 and 42 mm Hg, as measured by inline capnography. Lead II of the surface electrocardiogram was monitored continuously. Temperature was maintained at 37.5 to 39.0°C. Vital signs and biochemical variables (arterial blood gas, hematocrit, and

Table 1
Baseline Characteristics of the Animals, Immediately Before Cyanide Infusion

Characteristics	IV Hydroxocobalamin ($n = 12$)	IO Hydroxocobalamin ($n = 12$)
Weight, kg	48 (± 3)	50 (± 4)
Heart rate, beats/min	85 (± 17)	88 (± 27)
Systolic blood pressure, mm Hg	110 (± 7)	108 (± 11)
MAP, mm Hg	86 (± 6)	87 (± 8)
Cardiac output, L/min	5.0 (± 1.6)	4.6 (± 0.9)
Systemic vascular resistance, dynes-sec/cm ⁵	1,347 (± 313)	1,466 (± 238)
pH	7.44 (± 0.03)	7.47 (± 0.06)
Bicarbonate, mEq/L	28 (± 2)	27 (± 2.4)
Lactate, mmol/L	1.3 (± 0.7)	1.3 (± 0.6)

Data are presented as mean (\pm SD)

IO = intraosseous; IV = intravenous; MAP = mean arterial pressure.

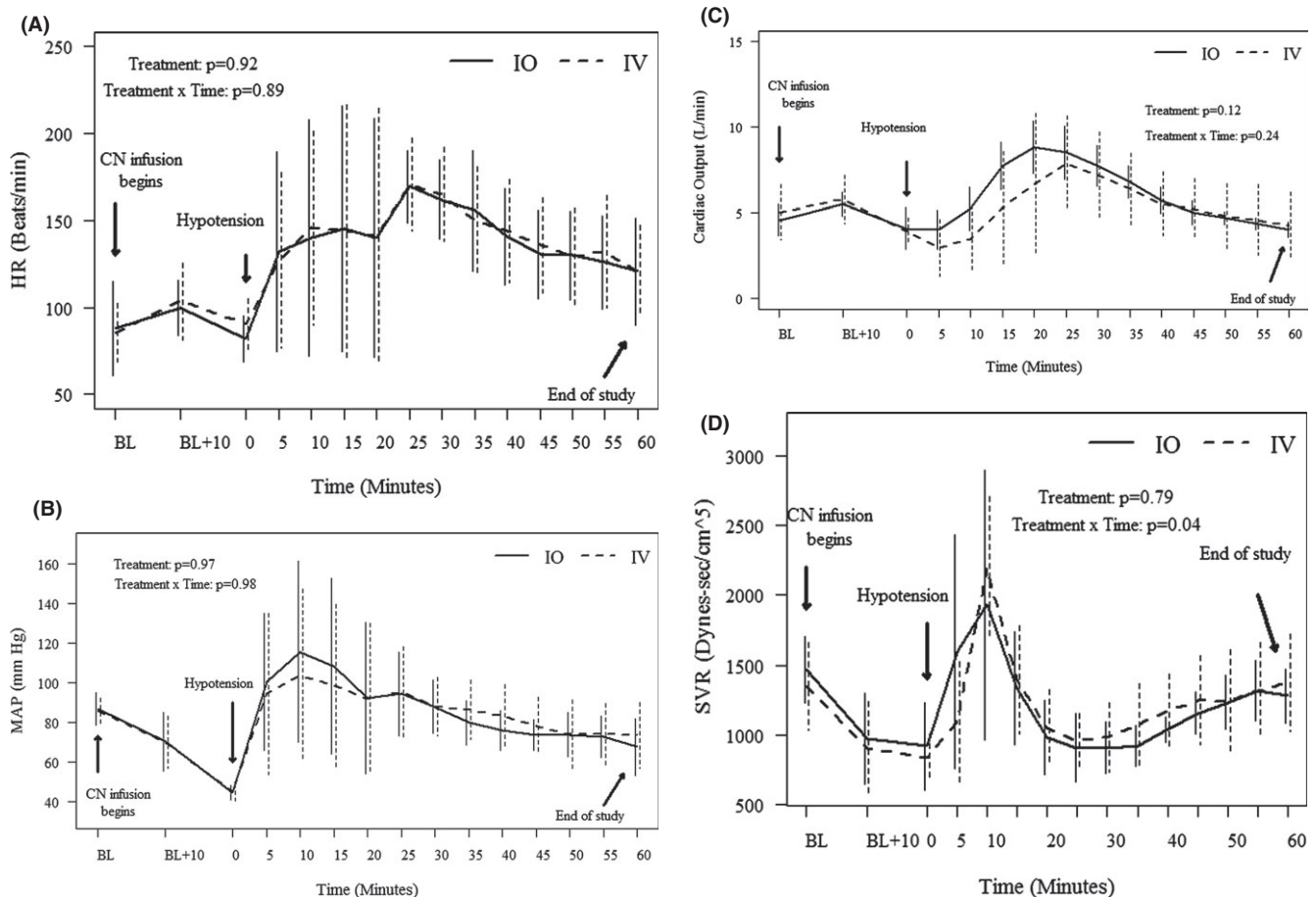


Figure 1. Hemodynamic measurements measured in the animals over time until the end of the experiments. IV cyanide infusion was started at baseline and stopped at hypotension. Antidote was administered at hypotension. (A) Graph of heart rate plotted against time over the experiment. (B) Graph of cardiac output plotted against time over the experiment. (C) Graph of mean arterial pressure plotted against time over the experiment. (D) Graph of systemic vascular resistance plotted against time over the experiment. IO hydroxocobalamin (solid line), $n = 10$; IV hydroxocobalamin (dashed line), $n = 10$; error bars represent SDs. BL = baseline; CN = cyanide; HR = heart rate; IO = intraosseous; IV = intravenous; MAP = mean arterial pressure; SVR = systemic vascular resistance.

electrolytes) were measured at baseline and during the study procedure.

Study Protocol

Invasive hemodynamic variables were measured with an eight-French Swan-Ganz CCOMbo pulmonary artery catheter (Model 746HF8) and the Edwards Vigilance II monitor (Edwards Lifesciences). Measurements included continuous cardiac output, systemic vascular resistance, mixed venous oxygen saturation (SVO₂), central venous pressure (CVP), pulmonary artery pressure, and core temperature. The catheter ports were flushed with saline and the catheter was placed via cutdown in the right external jugular. Aortic pressure was measured continuously through the femoral artery. An 8.5-French introducer (Arrow) was placed in the carotid artery for laboratory sampling and another was placed in the femoral vein for medication administration. The IO needle (EZ-IO, Vidacare) was placed in the proximal tibia and confirmed to be in the marrow by fluoroscopy and by aspiration.^{16,17} Four milliliters of heparinized saline was infused into the IO catheter to maintain patency. Each animal received a warmed saline IV bolus (15 mL/kg) during procedure setup. Heparin (100 units/kg) was

administered IV after catheters were inserted. The Fabius GS anesthesia data collection software was used for data acquisition at 1-minute intervals.

Baseline biochemical measurements included oxygen saturation, partial pressure of carbon dioxide in the blood (PaCO₂), partial pressure of oxygen in the blood (PaO₂), pH (ABL 800 Flex blood gas analyzer, Radiometer America), methemoglobin and hemoglobin (OSM3 hemoximeter, Radiometer), and electrolytes (Piccolo chemistry analyzer, Abaxis). We could not measure nitric oxide directly because the orange color of hydroxocobalamin interfered with the colorimetric chemiluminescent analyzer (Sievers Nitric Oxide Analyzer, GE). Instead we measured nitrotyrosine, a downstream, validated surrogate of nitric oxide formation.^{18,19} Nitrotyrosine (Northwest Life Science Specialties, LLC) was detected by enzyme-linked immunosorbent assay (ELISA). Cytokines were also measured by ELISA (R&D Systems). Near infrared spectrophotometry (NIRS; Somanetics, INVOS, oximeter cerebral/somatic, Model 5100C) was performed on the kidney and brain to measure continuous tissue oxygen saturation. Bed-side ultrasound (Zonare, Model 70111-00RC) was used to identify the kidney and brain placement of the pads

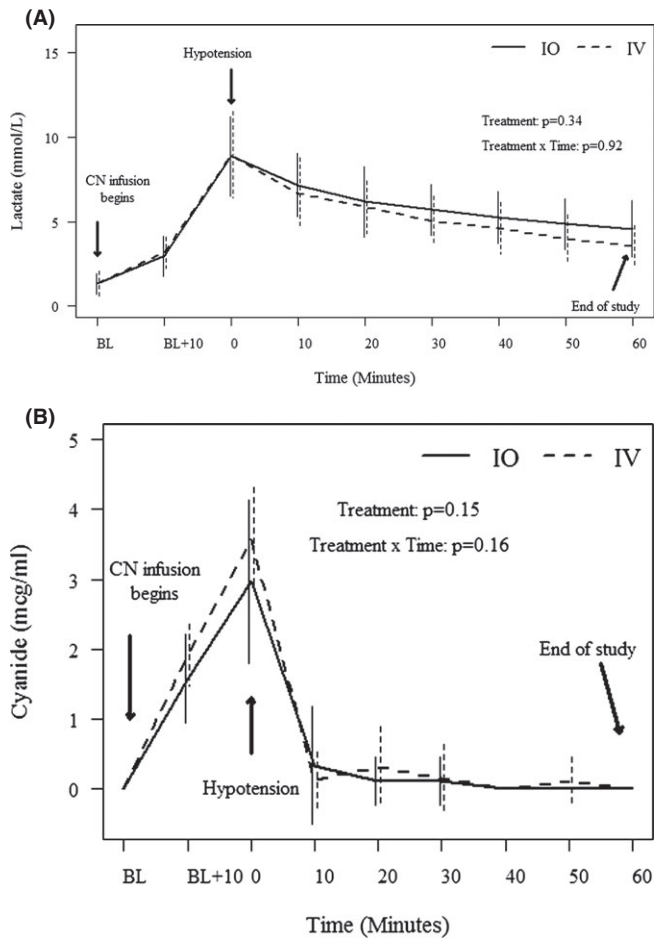


Figure 2. Laboratory measurements measured in the animals over time until the end of the experiments. IV cyanide infusion was started at baseline and stopped at hypotension. Antidote was administered at hypotension. (A) Graph of lactate plotted against time over the experiment. (B) Graph of blood cyanide levels plotted against time over the experiment. IO hydroxocobalamin (solid line), $n = 10$; IV hydroxocobalamin (dashed line), $n = 10$; error bars represent SDs. IO = intraosseous; IV = intravenous.

on shaved, nonpigmented skin. Brain microdialysis was also performed, and samples were frozen for future analysis.

Animals were acclimated for 10 minutes before the experiment and then isoflurane was reduced to 1.5%. The animals were then randomized to one of two arms: IV hydroxocobalamin or IO hydroxocobalamin. A 4% potassium cyanide mixture (potassium cyanide, Sigma

Aldrich; normal saline) was infused continuously until severe hypotension developed, defined as a 50% reduction in baseline mean arterial pressure (MAP) for 1 minute. In our previous experiments, we have found this dose effective in causing severe hypotension and 100% lethality if untreated, while allowing animals to recover with antidotal treatment.⁵

When a 50% reduction in MAP was achieved, the animals were administered IV hydroxocobalamin (150 mg/kg) or IO hydroxocobalamin (150 mg/kg) IV as a bolus over 2 to 3 minutes (depending on the pig's weight).⁵ Each animal received the antidote in an equal volume of 180 mL.⁵ The dose and infusion duration for hydroxocobalamin were based on our previously published model and other large animal studies.^{5-7,20} Ten milliliters of saline was infused before and after each drug administration. Also at hypotension, FiO_2 was increased to 1.0 and a 20 mL/kg warmed (38 °C) saline bolus was infused to replicate clinically relevant resuscitative treatments. The animals were then monitored for 60 minutes after severe hypotension was reached. Death was defined as a MAP less than 20 mm Hg for 5 minutes, and all animals were observed for at least 20 minutes after antidote administration for delayed improvement in vital signs. The animals were euthanized with IV administration of 100 mg/kg sodium pentobarbital.

Whole blood cyanide levels were measured using spectrophotometry at a referral laboratory (Diagnostic Center for Population and Animal Health, Michigan State University, Lansing, MI) and the methods are published in previous reports.^{5,6,21} Plasma hydroxocobalamin and cyanocobalamin levels were measured using liquid chromatography and tandem mass spectrometry.²²

Outcome Measures

The primary outcome measure was the change in MAP after antidotal treatment from onset of hypotension (time zero) to 60 minutes. This outcome was defined before the study. We also compared cardiac output, heart rate, SVO_2 , pH, lactate, base excess, serum bicarbonate, cyanide, nitrotyrosine levels, and inflammatory markers. Vital signs, hemodynamic measurements, and NIRS of the brain and kidney were recorded at 1-minute intervals and analyzed at 5-minute intervals. Serum blood sampling was taken at baseline; 10 minutes after cyanide infusion start; at onset of hypotension (50% of baseline MAP); and at 10, 20, 30, 40, 50, and 60 minutes after hypotension.

Table 2
Cyanide Dosing and Interval Data at Hypotension, Immediately Before Antidote Administration

Characteristics at Hypotension (MAP < 50% of Baseline)	IV Hydroxocobalamin ($n = 12$)	IO Hydroxocobalamin ($n = 12$)
Cyanide dose, mg/kg	5 (± 1.1)	5.8 (± 1.4)
Time to hypotension, min:sec	30:44 ($\pm 6:41$)	35:56 ($\pm 8:37$)
MAP at hypotension, mm Hg	45 (± 4)	45 (± 4)
Lactate, mmol/L	9 (± 2.54)	8.9 (± 2.4)
Cyanide level, $\mu\text{g/mL}$	3.6 (± 0.7)	3 (± 1.2)
pH	7.36 (± 0.06)	7.35 (± 0.08)

Data are presented as mean (\pm SD).
MAP = mean arterial pressure.

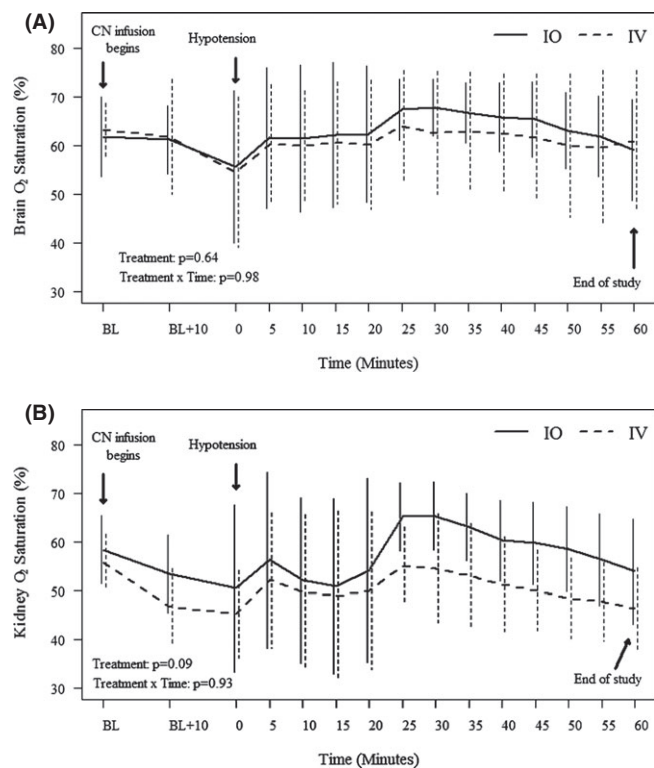


Figure 3. Cerebral and renal oxygen saturation measured in the animals over time until the end of the experiments. IV cyanide infusion was started at baseline and stopped at hypotension. Antidote was administered at hypotension. (A) Graph of brain oxygen saturation plotted against time over the experiment. (B) Graph of renal oxygen saturation plotted against time over the experiment. IO hydroxocobalamin (solid line), $n = 10$; IV hydroxocobalamin (dashed line), $n = 10$; error bars represent SDs. IO = intraosseous; IV = intravenous.

Data Analysis

Values for MAP and the main outcome variables were compared between groups from time zero through 60 minutes using a repeated-measures linear model adjusted for the fixed effects of treatment group, time, and the treatment by time interaction, with an autoregressive covariance structure assumed. Animals that died before completion of the study were excluded from this analysis. Prior to the initiation of the study protocol, a 50% increase in MAP above the time zero value (hypotension) was defined as clinically significant in regard to recovery from cyanide toxicity. Based on a standard deviation (SD) of 4.4 mm Hg derived from our previous studies, we calculated that we would need 10 animals in each group to provide a power of 80% with an alpha of 0.05, which was not corrected for multiple comparisons. Sample size calculations were performed with Stata (version 11.0). Twenty-four animals were used with the expectation of early demise before conclusion of the experiment in 10% to 15% of the animals.

Secondary variables (cardiac output, heart rate, SVR, SVO₂, and NIRS) were compared between groups at times zero through 60 minutes using repeated-measures analysis of variance. Similarly, values for arterial blood pH, lactate, cyanide, nitrotyrosine, bicarbonate, base excess, and potassium concentrations for times zero to 60 minutes were also compared between groups using

a repeated measures linear model. Correlation was assessed through univariable linear regression on actual measures and percent baseline, modeling the MAP, cardiac output, and SVO₂ as predictors of brain and kidney spectroscopy.

Post hoc analysis at individual time points was performed using univariate analysis only if the multivariate test showed a significant difference between groups. Statistical significance was set at $p < 0.05$, and all p -values represent two-tailed calculations. Statistical analyses were performed using SPSS version 16.

RESULTS

At baseline all of the physiologic parameters, including weight, heart rate, blood pressure, cardiac output, vascular resistance, and pH were comparable between both IV and IO groups (Table 1). At hypotension, mean MAP (IV 45 mm Hg, IO 45 mm Hg), blood cyanide (IV 3.5 $\mu\text{g}/\text{mL}$, IO 3.1 $\mu\text{g}/\text{mL}$), and lactate levels (IV mmol/L 8.9, IO 8.8 mmol/L) were similar between groups (Figures 1 and 2 and Table 2)

At the conclusion of the study, 10 out of 12 animals in the IV group and 10 out of 12 in IO group survived ($p = 1.0$). Deaths in both groups occurred within 5 minutes after drug administration. The surviving animals in both groups had a similar return to baseline MAP ($p = 0.997$) from hypotension. No significant differences were detected between groups for cardiac output, SVO₂, and SVR ($p > 0.4$) or for bicarbonate, pH, and lactate levels ($p > 0.8$). Whole blood cyanide levels remained undetectable after hydroxocobalamin administration in both groups ($p = 1.0$). Serum nitrotyrosine initially rose during cyanide infusion in all animals, and then decreased in both after hydroxocobalamin infusion ($p > 0.5$). Cerebral and renal oxygenation, as measured by NIRS, decreased in parallel to MAP during cyanide infusion and increased after antidote infusion, but did not correlate with MAP, cardiac output, or mixed venous saturation (Figure 3 and 4). Serum levels of the inflammatory markers (tumor necrosis factor [TNF]- α , interleukin [IL]-1 β , IL-6, IL-8, IL-10, and IL-12) were consistent between groups and increased by 200% to 400% from baseline (Figure 5).

We did not identify a difference in complications related to infusion between the groups. Skin discoloration was the same. IO infiltration did not occur in any animals. In five animals we performed necropsy of the extremity where the IO needle placed. The veterinarian pathologist did not detect unusual or clinically concerning necrosis or tissue damage at the sites of IO hydroxocobalamin.

DISCUSSION

In our swine model of severe cyanide toxicity, we found no difference between IO hydroxocobalamin and IV administration.^{6,7} This result supports previous research that found that the pharmacokinetics of IO hydroxocobalamin administration were similar to IV administration and were equally safe.^{4,11} Our study is novel in that we evaluated the effectiveness of IO hydroxocobalamin in animals acutely intoxicated with cyanide. In addition,

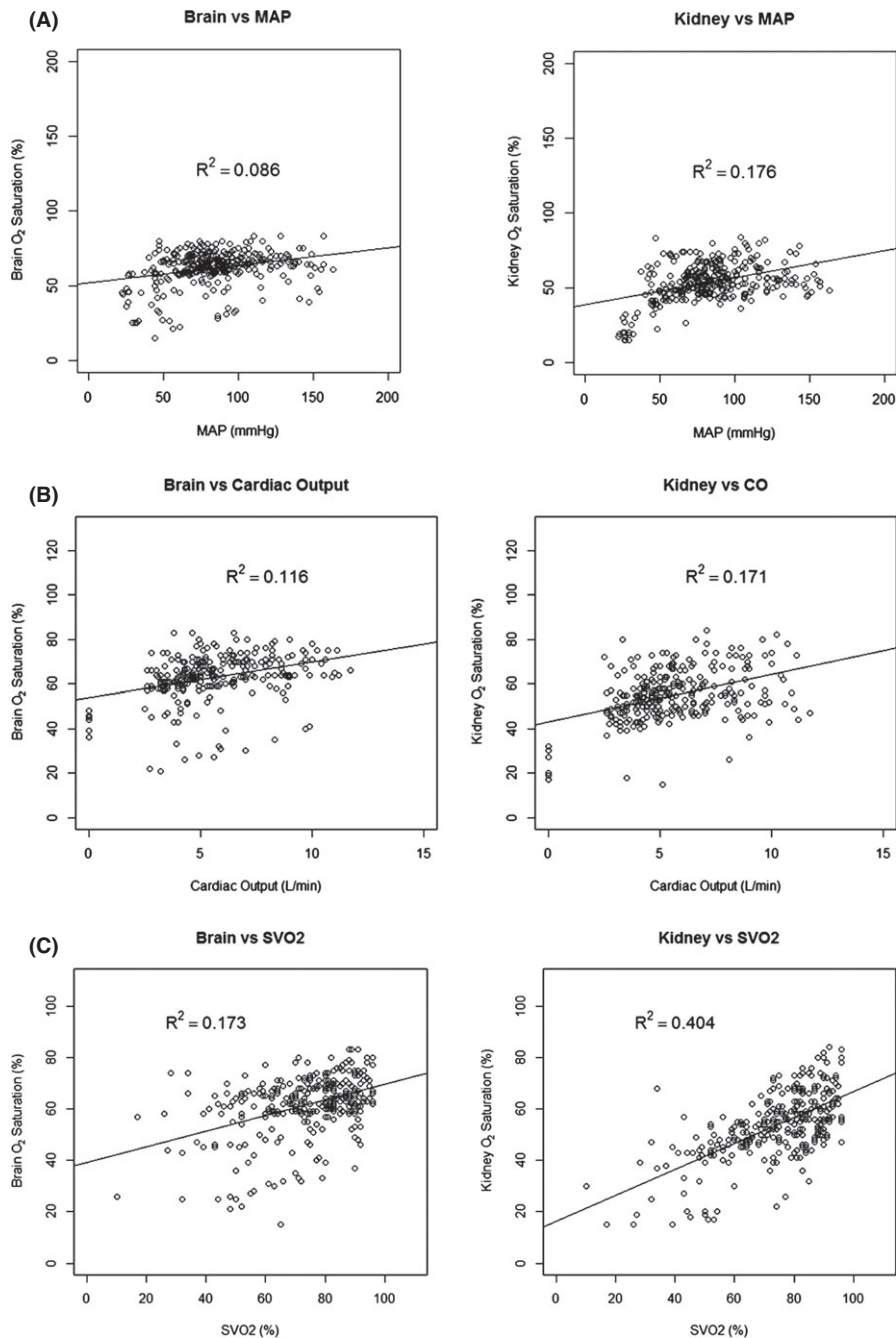


Figure 4. Correlation plot of cerebral and renal oxygenation with mean arterial pressure (MAP), cardiac output (CO), and mixed venous saturation (SVO₂). (A) Plot of brain and kidney oxygen saturation plotted against mean arterial pressure. (B) Plot of brain and kidney oxygen saturation plotted against cardiac output. (C) Plot of brain and kidney oxygen saturation plotted against mixed venous saturation.

we employed a larger dose of hydroxocobalamin and infused it over a shorter period of time as would be used in the emergent treatment of cyanide toxicity.

In mass casualty situations, whether on the battlefield, in a terrorist attack, or for the treatment of fire victims, non-IV routes of administration are needed for the acute treatment of cyanide poisoning. IO administration may be an option and is already recommended as a second line of drug administration by the American Heart Association.^{23,24} In its favor, IO catheter placement has been shown to have a high success rate, is simple, and

is commonly practiced in the prehospital and hospital settings.^{15,25,26}

In addition to evaluating the efficacy of IO hydroxocobalamin, we used near infrared spectroscopy, which is a continuous noninvasive assessment of tissue perfusion and oxygen delivery in trauma care and hemorrhage.²⁷ NIRS has shown benefit in emergency settings, but use of NIRS has not been evaluated for chemical-induced shock and more specifically with cyanide toxicity. In our study, NIRS generally paralleled MAP, but was not predictive of hypotension.

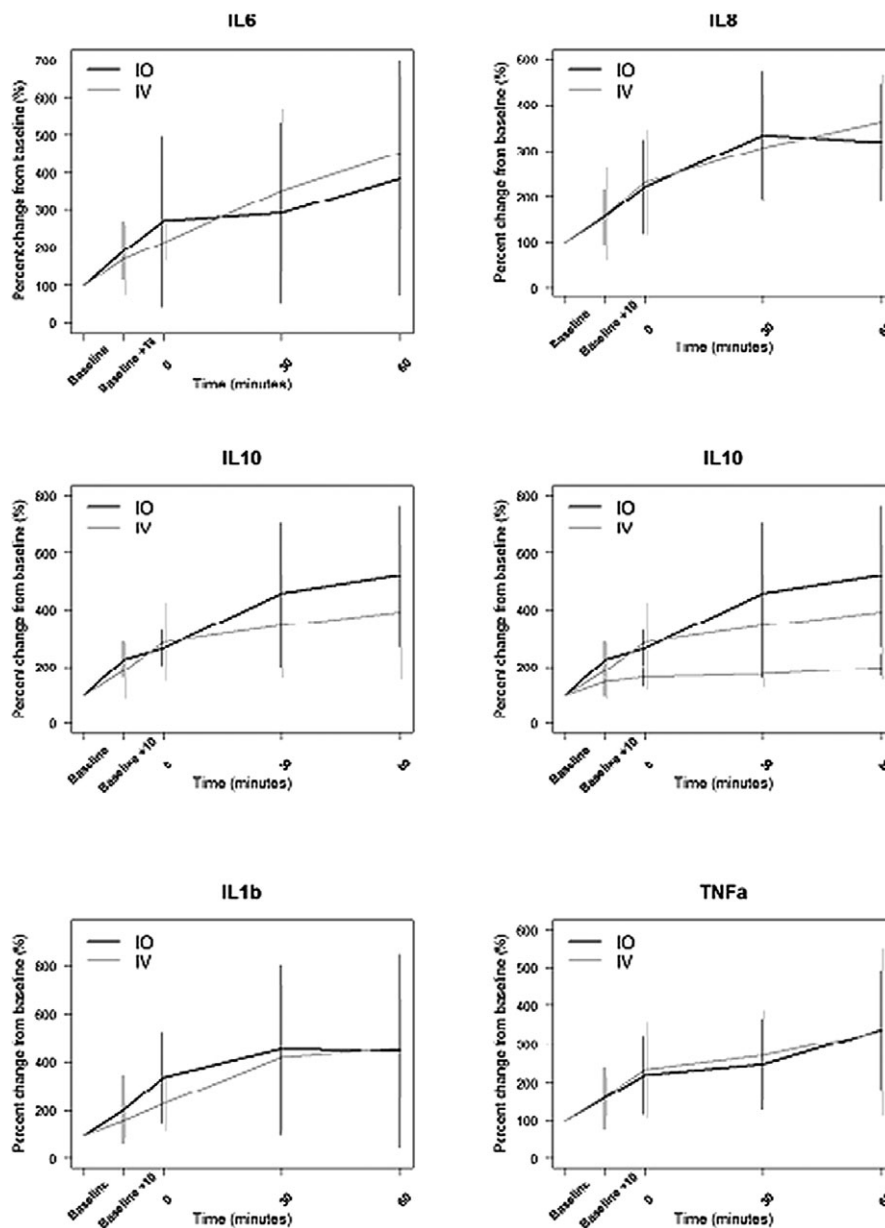


Figure 5. Plot of serum cytokine measurements as a percentage of baseline over time until the end of the experiments. IV cyanide infusion was started at baseline and stopped at hypotension. Antidote was administered at hypotension. IO hydroxocobalamin (solid line), $n = 10$; IV hydroxocobalamin (dashed line), $n = 10$; error bars represent SDs. IV = intravenous; IO = intraosseous.

Cyanide infusion induced the production of different sets of inflammatory markers, and the increased expressions were of the same magnitude for both IO and IV routes. $\text{TNF-}\alpha$, IL-6, IL-1 β , and IL-8, a key neutrophil chemoattractant, were noted to increase as soon as 10 minutes following cyanide infusion. Of interest, IL-12, a Th-1 cytokine, and IL-10, an anti-inflammatory interleukin,²⁸ were also induced by cyanide.²⁹ At present it is not clear how cyanide initiates its inflammatory effects, although at least two potential mechanisms can be proposed: a direct effect in which cyanide-induced hypoxia activates cytokine gene expression and an indirect mechanism in which cyanide acts through interactions with nitric oxide. Nitric oxide is a well-documented modulator of the immune system that has

been implicated in *in vitro* as well as *in vivo* inductions of multiple cytokines, and its effects may be concentration dependent.³⁰ Another intriguing observation of the present study was the release of IL-10, which may represent a compensatory response to downregulate the activity of cyanide-induced proinflammatory cytokines, a situation that has also been documented for inflammatory conditions such as sepsis,³¹ delayed type hyperactivity, or trauma.^{32–34}

Based on the results of our study, hydroxocobalamin infused by IO may be effective for severe cyanide toxicity. Future studies may report human effects and outcomes of IO-infused hydroxocobalamin and to ensure there are no long-lasting injuries from IO hydroxocobalamin administration.

LIMITATIONS

This animal model does not reproduce human toxicity exactly. However, the swine model has been used in previous studies of cyanide toxicity and of resuscitation and cardiac arrest.^{15,31,32} The swine cardiovascular system is also analogous to humans.^{5,32,33} Although the pig appears to be an acceptable model for IO needle placement, differences in physiology may make extrapolations to humans problematic. The intramedullary volume of swine tibia is smaller than that in adult humans and the distance from the tibial plateau to the heart is shorter.³⁴ We used maximal doses of each antidote to achieve maximal effects similar to previous studies.^{5,6,20} Lower doses of the antidotes may have had different outcomes. We used potassium cyanide; however, the potassium dose infused was small. The 50-kg animals received 2 mEq of potassium in approximately 30 minutes. We used IV cyanide instead of inhalational cyanide, the more common route of human exposure. Both routes rapidly induce toxicity, but the IV route provided a controlled toxicity, which may be more repeatable in an experimental setting than the uncontrolled absorption through an inhalational model of cyanide poisoning. In addition, the inhalational route could put the research staff at greater risk than the IV route due to undetected leaks in the ventilation system.^{20,35} We also used objective clinical endpoints, reduction in blood pressure, and measured cyanide levels, to ensure that toxic concentrations and cyanide dose were similar to or greater than those reported in humans.³⁶ The error bars are much longer just after antidote administration due to the greater clinical variability each animal had in response to reversal of hypotension during this dynamic period. We did not have a contemporaneous control group and we had an open-label design. Finally, because our animals were mechanically ventilated, we did not study the effects of our treatments on cyanide-induced apnea that is an early sign of cyanide toxicity.

CONCLUSIONS

We found no difference in the efficacy of intravenous versus intraosseous hydroxocobalamin in the treatment of severe cyanide toxicity in a validated porcine model. Intraosseous hydroxocobalamin may be as effective as the intravenous route in treatment of acute, severe cyanide toxicity

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