

Original Article

Outcomes after the administration of hydroxocobalamin

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Abstract: *Background:* Hydroxocobalamin is frequently administered to patients after injuries sustained during structure fires or fires in enclosed spaces, prior to confirming inhalation injury with bronchoscopy. Hydroxocobalamin is generally considered safe. However, over the last several years, the safety of hydroxocobalamin has been called into question by case reports of crystalline nephropathy and interference with renal replacement therapies. *Objectives:* The aim of this project was to describe the population in which hydroxocobalamin was administered and assess clinical outcomes such as mortality and need for renal replacement therapy. We hypothesized that there is a relationship between the administration of hydroxocobalamin and the development of acute kidney injury (AKI). *Methods:* This was a retrospective chart review that was approved by our institution's research and regulatory compliance division as a performance improvement (PI) project (H-19-019nr). All patients admitted to the burn ICU at a large, government medical center between July 1, 2016 and April 30, 2019 were considered for inclusion. Patients were included if they received hydroxocobalamin after burn ICU admission. Patients who received hydroxocobalamin in the pre-ICU or pre-hospital setting were not included. Data were collected from the electronic medical record and included demographic information, number of hydroxocobalamin doses administered, burn size (%TBSA), presence and grade of inhalation injury, lactate levels during the first 72 hours of hospitalization, carboxyhemoglobin levels, duration of mechanical ventilation, and in-hospital mortality. Development of acute kidney injury (AKI) as per the AKIN criteria, as well as need for and duration of continuous renal replacement therapy (CRRT) were also collected. *Results:* Thirty five patients received at least 1 dose of hydroxocobalamin after ICU admission; 31 patients received 1 dose and 4 patients received 2 doses. Twenty nine (82.9%) patients who received hydroxocobalamin in the ICU were diagnosed with inhalation injury via bronchoscopy. The median fluid resuscitation requirement was 7.4 mL/kg/%TBSA (IQR 4.6, 12.7). Twenty two (63%) patients who received hydroxocobalamin developed an acute kidney injury (AKI) during the first 72 hours of admission, with the average time from burn to AKI being approximately 20 hours. Twenty one (60%) patients required CRRT at some point during their hospital stay, with 42.8% of patients being initiated on CRRT during the resuscitation period. On average, lactate clearance occurred in 34.6 hours; 11 (31.4%) patients did not clear lactate within 72 hours. One patient had a carboxyhemoglobin level greater than 10% on admission and 4 patients had a carboxyhemoglobin level greater than 3% on admission. The average time to carboxyhemoglobin level less than 3% was 3.4 ± 2.6 hours. The average duration of mechanical ventilation was 11 ± 7 days. Ten (28.9%) patients died during their hospital stay. *Conclusions:* Most patients who receive at least 1 dose of hydroxocobalamin after ICU admission developed AKI within the first 72 hours, with 42.8% of patients requiring CRRT during the initial resuscitation period. One-third of patients who received hydroxocobalamin after ICU admission died during their hospital stay. Further studies on the relationship between the administration of hydroxocobalamin and the development of AKI and in-hospital mortality are warranted.

Keywords: Cyanide toxicity, hydroxocobalamin, acute kidney injury, renal replacement therapy, inhalation injury

Introduction

Cyanide poisoning is a leading cause of death in smoke-related inhalation injury. Inhalation injury occurs in up to 30% of all fire-related injuries. Of the approximately 3,400 fire-related deaths in the United States annually, 60-80%

are thought to be associated with inhalation injury [1-3]. Prior to 2006, the only available treatment for cyanide toxicity was the three-agent cyanide antidote kit which was comprised of sodium thiosulfate, amyl nitrite, and sodium nitrite. Drawbacks to this treatment regimen include unpredictable induction of methemoglobinemia.

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moglobinemia, vasodilation, and slow onset of action [4]. Hydroxocobalamin is currently the preferred therapy for suspected cyanide toxicity due to its favorable side-effect profile compared to the three agent antidote kit. Additionally, hydroxocobalamin is thought to have a faster onset of action than sodium thiosulfate, making it ideal for use in emergency situations [5].

Hydrogen cyanide (HCN) is produced by combustion of nitrogen- and carbon-containing compounds. These include synthetic materials such as polyurethane, acrylics, and nylon; and natural materials such as wood, silk, cotton, and wool. HCN inhibits oxidative phosphorylation by binding the ferric iron of cytochrome C oxidase a3 within the mitochondrial complex, resulting in impaired oxygen use and a shift to anaerobic metabolism [6, 7]. This functional cellular anoxia results in lactate generation, metabolic acidosis, and end-organ dysfunction [8].

Hydroxocobalamin, a vitamin B12 precursor, was approved by the United States Food and Drug Administration in 2006 for the treatment of cyanide poisoning. The cobalt moiety of hydroxocobalamin binds the cyanide anion. This results in the generation of cyanocobalamin, vitamin B12, which is then renally excreted [9, 10]. Hydroxocobalamin is generally considered safe and well-tolerated, with the most common side effects being intense red-purple discoloration of skin, plasma, urine, and tears, and transient hypertension [11, 12]. However, over the last several years, the safety of hydroxocobalamin has been called into question by case reports of crystalline nephropathy and interference with renal replacement therapies [13-15]. The aim of this project was to describe the population in which hydroxocobalamin was administered and assess clinical outcomes such as mortality and need for renal replacement therapy. We hypothesized that there is a relationship between the administration of hydroxocobalamin and the development of acute kidney injury (AKI).

Methods

This project was approved by our institution's research and regulatory compliance division as a performance improvement (PI) project (H-19-019nr). As this project was approved as

a retrospective performance improvement project, informed consent was not required. All privacy and ethics standards were met. This was a retrospective chart review that included all patients admitted to the burn intensive care unit (ICU) between July 1, 2016 and April 30, 2019. Patients were included if they received hydroxocobalamin after burn ICU admission. Patients who received hydroxocobalamin in the pre-ICU or pre-hospital setting were not included due to inconsistencies in data reporting. Additionally, subjects with pre-existing renal failure were excluded.

Data collection

Data were collected from the electronic medical record and included demographic information, number of hydroxocobalamin doses administered, burn size (%TBSA), presence and grade of inhalation injury, lactate levels during the first 72 hours of hospitalization, carboxyhemoglobin levels, need for and duration of continuous renal replacement therapy (CRRT), duration of mechanical ventilation, and in-hospital mortality.

Statistical analysis

Descriptive statistics (median [IQR] and n [%]) were performed using SPSS version 22 (IBM, Armonk, NY). Data that were normally distributed were reported as means \pm SD, and data that were not normally distributed were reported as medians and interquartile ranges (IQR). Fisher's exact test was used to compare incidence of AKI between patients who had inhalation injury (any grade) and those who did not. Statistical significance was set at $P < 0.05$.

Results

Demographics

Table 1 shows the demographic characteristics of the patients who were included. Thirty-five patients received at least 1 dose of hydroxocobalamin after ICU admission; 31 patients (88.6%) received 1 dose and 4 patients (11.4%) received 2 doses. **Table 1** shows the demographic characteristics of those included. Patients were a median of 46 years old (IQR 34.5, 65.8 years) with a median burn size of 18% TBSA (IQR 8.25, 32.5% TBSA). Twenty-nine patients (82.9%) who received hydroxoco-

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Table 1. Demographic characteristics

Characteristic	N = 35
Male gender, n (%)	23 (65.7)
Age, years, median (IQR)	46 (34.5, 65.8)
Burn size, %TBSA, median (IQR)	18 (8.35, 32.5)
Inhalation injury, n (%)	29 (82.9)
Grade 1	10 (28.9)
Grade 2	13 (37.1)
Grade 3	4 (11.4)
Grade 4	2 (5.7)
24-hour fluid resuscitation requirements, mL/kg/%TBSA, median (IQR)	7.4 (4.6, 12.7)
Admission lactate, mmol/L, mean \pm SD	4.4 \pm 2.3
Receipt of >1 dose of hydroxocobalamin, n (%)	4 (11.4)

Table 2. Incidence of AKI by inhalation injury status

	No inhalation injury (n = 6)	Inhalation injury (n = 29)
No AKI	3 (50%)	10 (34.5%)
AKI	3 (50%)	19 (65.5%)
Total	6 (100%)	29 (100%)

balamin in the ICU were diagnosed with inhalation injury via bronchoscopy. The median 24-hour fluid resuscitation requirement was 7.4 mL/kg/%TBSA (IQR 4.6, 12.7) or 128.5 mL/kg (IQR 92.8, 22.5).

Patients had a median ICU length of stay (LOS) of 15 days (IQR 5, 28 days), with a hospital LOS of 21 days (IQR 9, 37 days). The average duration of mechanical ventilation was 11 \pm 7 days. Thirteen (37.1%) patients died during their hospital stay. One patient who received hydroxocobalamin and did not have inhalation injury died; this patient had a burn size of 95% TBSA.

AKI and need for CRRT

Twenty-two patients (63%) who received hydroxocobalamin developed AKI, as per the AKIN criteria, during the first 72 hours of admission. Six (17.1%) patients had stage 1 AKI, 1 (2.9%) patient had stage 2 AKI, and 15 (42.9%) patients had stage 3 AKI. The median time from burn to AKI was 15.1 hours (IQR 11.8, 21.3 hours). Twenty-one patients (60%) required CRRT during their hospital stay; 42.8% of patients were initiated on CRRT during the first 24 hours of admission. Acidemia

was the most common indication for CRRT (34.3%), followed by volume management (28.6%), hyperkalemia (22.9%), and uremia (11.4%). No patients required renal replacement therapy or hemodialysis after ICU discharge. **Table 2** shows AKI incidence by inhalation injury status. The incidence AKI was not significantly different between patients who had inhalation injury and those who did not (65.5% of subjects with inhalation injury vs 50% without inhalation injury, $P = 0.648$).

Lactate clearance

The mean admission lactate level was 4.4 \pm 2.3 mmol/L. On average, lactate clearance, as defined by 2 consecutive lactate levels less than 2 mmol/L, occurred in 34.6 hours; 11 (31.4%) patients did not clear lactate within 72 hours. One patient had a carboxyhemoglobin level greater than 10% on admission and 4 patients had a carboxyhemoglobin level greater than 3% on admission.

Discussion

We conducted a retrospective chart review to describe the population in which hydroxocobalamin is administered and to investigate whether the use of hydroxocobalamin was associated with the development to AKI. We found that 63% of patients who received hydroxocobalamin after ICU admission developed AKI, with 60% of patients requiring renal replacement therapy during their ICU stay. In the current review, incidence of AKI was not significantly different between subjects who had inhalation injury and those who did not,

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suggesting that independent of inhalation injury, the use of hydroxocobalamin may be associated with AKI.

Hydroxocobalamin is generally considered safe and well-tolerated, with the most common side effects being intense red-purple discoloration of skin, plasma, urine, and tears, and transient hypertension [11].

Due to serum discoloration, commonly ordered laboratory tests such as serum chemistries must be interpreted with caution after administration of hydroxocobalamin [6, 16]. In addition to variance in serum studies, hydroxocobalamin administration has been reported to interfere with certain renal replacement therapies that incorporate photo-detection technology [15, 17].

Recently, safety concerns have been raised regarding a potential association between hydroxocobalamin administration and generation of oxalate and subsequent nephropathy. A case series published as a Letter to the Editor in 2016 described two patients who received hydroxocobalamin for suspected cyanide toxicity in the setting of inhalation injury. Both patients developed acute kidney injury requiring renal replacement therapy. Renal biopsy of both patients revealed evidence of acute tubular necrosis with the presence of renal tubule calcium oxalate crystals. A follow-on prospective observational study, presented in the same Letter, demonstrated elevated urine oxalate levels in patients who received hydroxocobalamin. A subsequent retrospective review of mechanically ventilated burn patients showed that hydroxocobalamin significantly increased the odds of developing AKI (OR: 5.8 [1.6-20.7]) and needing CRRT (OR: 4.3 [1.09-17]). However, the comparison group was not exposed to smoke inhalation or cyanide therapy, and the work did not address other factors that may have contributed to the development of AKI, such as vasopressors, infections, pre-existing renal dysfunction or pre-existing diseases that increase risk of renal injury [18]. Following these Letters to the Editor, a multicenter retrospective study was conducted to examine the risk of AKI, major adverse kidney events (MAKE), and survival after the administration of hydroxocobalamin. Thirty nine percent of subjects who received hydroxocobalamin developed AKI, 25% of

which developed severe AKI within the first week of hospitalization. Despite this, hydroxocobalamin was not associated with increased risk of MAKE [19]. Additionally, a case reports of patients developing oxalate nephropathy when hydroxocobalamin has been used for refractory vasoplegia was recently published. In a patient undergoing concomitant heart and kidney transplants, hydroxocobalamin was administered for three times during the initial transplant operation and the patient subsequent ICU stay for refractory vasoplegia. Despite adequate immunosuppression, the renal graft never fully functioned. On post-transplant day 21, a renal biopsy was taken, which showed oxalate crystal nephropathy [20].

Interestingly, a case series of two patients with severe anoxic brain injury related to inhalation injury from house fires who went for organ procurement demonstrated intense discoloration of procured organs, including kidneys. Renal biopsy of one of the two patients demonstrated renal tubule oxalate crystals which were not present on a 6-week follow-up biopsy after transplant. Neither of the recipients required ongoing renal replacement therapy [14].

Currently there are no rapid bedside or point-of-injury confirmatory tests for cyanide poisoning available in the United States. As such, treatment decisions rely on surrogates of cyanide toxicity including metabolic acidosis, elevated serum lactate, and non-specific clinical signs and symptoms including hypotension and end organ dysfunction [14]. Due to the lack of readily available confirmatory tests, we suspect that many patients receive hydroxocobalamin treatment in the absence of toxic levels of cyanide. Historically, hydroxocobalamin was not thought to cause serious adverse reactions.

In light of recent case series and the current project, further research is needed to determine if hydroxocobalamin is truly associated with oxalate production and the risk of AKI. It has been hypothesized that patients with burn injury may have low tubular fluid flow secondary to severe dehydration initially after burn injury and that this low-flow state may promote tubular deposits of oxalate crystals [21]. However, this has never been proven. Still, many unanswered questions remain. Is oxalate

nephropathy present in patients with burn injury who have not received hydroxocobalamin? Can the patients who will develop oxalate nephropathy or AKI after the administration of hydroxocobalamin be predicted? Additionally, can an ideal laboratory or point of care test be developed to better develop toxic levels of serum cyanide so that only the patients who are truly experiencing cyanide toxicity receive hydroxocobalamin? Lastly, what effects do multiple doses of hydroxocobalamin have on patient outcomes? All of these questions warrant further investigation.

The present review is limited, as it is a small, single-center and retrospective in nature. Subjects who received hydroxocobalamin prior to ICU admission (either in the field, en route, or in the emergency department) were not included. Additionally, other potential causes of AKI and the need for CRRT were not strictly evaluated.

Conclusion

Most patients who received at least one dose of hydroxocobalamin after ICU admission developed AKI within the first 72 hours, with 42.8% of patients requiring CRRT during the initial resuscitation period. Further studies on the relationship between the administration of hydroxocobalamin and the development of AKI and in-hospital mortality are warranted. Future studies need to address the relationship between hydroxocobalamin administration and oxalate generation and propose potential mechanism by which this occurs, as well as potential clinical implications of oxalate generation.

Disclosure of conflict of interest

The opinions or assertions contained herein are the private views of the authors, and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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