HYDROXOCOBALAMIN ADMINISTRATION AFTER INHALATION INJURY IS NOT ASSOCIATED WITH MESENTERIC ISCHEMIA

L'ADMINISTRATION D'HYDROXOCOBALAMINE APRÈS INHALATION DE FUMÉES N'EST PAS CORRÉLÉE AVEC UNE ISCHÉMIE MÉSENTÉRIQUE

Engwall A.J.,[1]✉ Blache A.,[2] Lintner A.,[2] Bright A.,[2] Kahn S.[3]

[1]Michigan State University, Lansing, Michigan, USA
[2]University of South Alabama, Mobile, Alabama, USA
[3]Medical University of South Carolina, Charleston, South Carolina, USA

SUMMARY. Hydroxocobalamin has been administered in the United States since 2006 by first responders and burn centers as a safe antidote for cyanide toxicity, a serious complication of smoke inhalation. There are no current contraindications to the use of this rescue measure. A recent retrospective French publication reported a potential correlation between hydroxcobalamin administration and acute mesenteric ischemia (AMI) in critically ill burn and inhalation injury patients. The purpose of this study is to characterize the risk of AMI related to hydroxocobalamin. A retrospective review of hydroxocobalamin administration among adult burn patients was conducted at a regional burn center over a 2-year period. Injury characteristics, demographics, and outcomes including presence of mesenteric ischemia (defined as presence of pneumatosis or perforation on CT scan or necrotic bowel on laparotomy) were recorded. Of 17 confirmed inhalation injuries, patients had a median (interquartile range) age, total body surface area (TBSA), and abbreviated burn severity (ABSI) index as follows: 60 (45, 65 IQR), 8.5 (1.8, 39 IQR), and 6 (5,7 IQR). Inhalation injury was diagnosed with bronchoscopy, carboxyhemoglobin, or clinical suspicion. Eighty-two percent of those with bronchoscopy had an inhalation grade of 2 or greater. None (0%) of the patients showed signs of mesenteric ischemia, tube feeding intolerance, pneumatosis/perforation on CT, or necrotic bowel on laparotomy. Aware of the study limitations, we conclude that hydroxocobalamin does not increase risk for AMI.

Keywords: cyanide toxicity, hydroxocobalamin, inhalation injury, acute mesenteric ischemia

RÉSUMÉ. *L'hydroxocobalamine (OHB12), antidote peu dangereux en cas d'intoxication cyanhydrique (complication grave de l'inhalation de fumées), est administrée depuis 2006 par les premiers secours étatsuniens. Il n'existe actuellement pas de contre- indication à son utilisation. Une étude rétrospective française récente a rapporté la possible association entre OHB12 et ischémie mésentérique (IM) chez des brûlés graves ayant inhalé des fumées. Cette étude se propose d'étudier cette éventuelle corrélation. Il s'agit d'une étude rétrospective conduite pendant 2 ans dans un CTB régional. Les caractéristiques démographiques, celles de la brûlure et l'évolution (en recherchant particulièrement une IM) ont été relevées. Le diagnostic d'IM était posé devant des images scannographiques évocatrices (pneumopéritoine, perforation digestive) ou la constatation per- opératoire d'une nécrose digestive. Dix- sept patients avaient une inhalation de fumées confirmée par endoscopie (dans ce cas, 87% des patients avec inhalation de fumées avaient des lésions de grade 2 ou plus) ou carboxyhémoglobine ou simple suspicion clinique. Leur âge médian était de 65 ans (Q1: 45, Q3 : 35), leur surface brûlés de 8,5% (Q1: 1,8, Q3 : 39), leur ABSI de 6 (Q1 : 5 ; Q3 : 7). Aucun patient n'a développé une IM ni une intolérance digestive. Bien que cette étude ait des limitations, nous concluons que OHB12 n'est pas un facteur de risque d'IM.*

Mots-clés : *inhalation de fumées, intoxication cyanhydrique, hydroxocobalamine, ischémie mésentérique*

✉ Corresponding author: Abigail Engwall, MD, previously affiliated at University of South Alabama Medical Center, Sparrow Hospital, Department of Surgery, 1215 East Michigan Ave Lansing, Michigan 48912, USA. Email: engwalla@msu.edu
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Introduction

Hydroxylated vitamin B12 was initially used in France in the 1980s to treat suspected cyanide toxicity.[1] In 2006, the FDA approved the use of hydroxocobalamin to treat cyanide toxicity that occurs with smoke inhalation.[2] Some limited data suggests this may be a life-saving intervention, but large-scale prospective studies in this area are lacking. A recent French study suggests hydroxocobalamin administration may be associated with an increased risk of non-occlusive acute mesenteric ischemia (AMI).[3]

AMI can be categorized into occlusive (related to emboli or thrombi in venous or arterial vasculature) or nonocclusive (related to vasospasm and low flow states).[4] Mortality has been reported in the acute setting to be between 60% and 80%.[5]

While AMI has high mortality, cyanide gas is produced as a product of combustion, particularly of plastics and synthetics,[6] which disrupts mammalian cells by uncoupling mitochondrial oxidative phosphorylation. Subsequently, a shift from aerobic to anaerobic metabolism.[7] High levels of cyanide vapor concentrations can cause death in 6-8 minutes.[8,9] Early symptoms may include vertigo, metallic taste, headache, nausea, tachypnea, tachycardia, hypertension, confusion and lethargy. These can devolve into cherry-red skin, hypotension, rhabdomyolysis, renal failure, hepatic necrosis, convulsions, respiratory arrest, and cardiac arrest.[10,11] As cyanide poisoning remains a deadly issue, there is a desire for an antidote with a safe profile.

Approximately 20-30% of hospitalized burn patients are estimated to have inhalation injury.[12,13] Multiple factors including chemical irritation of lung parenchyma, direct thermal injury to the upper airway, and system effects of toxin absorption such as cyanide and carbon monoxide, have been reported to markedly increase mortality.[7,14,15] In this way, an effective and safe antidote has the ability to reduce morbidity and mortality.

The few noted side effects of hydroxocobalamin are hypertension, headache, photosensitivity, infusion site reactions, and discoloration of the skin (which is suboptimal in assessing extent of skin injury).[7,16] Not only does hydroxocobalamin have no current contraindications, but the benefits and applications are increasing. Prehospital administration of hydroxocobalamin for smoke inhalation has been associated with better than expected survival rates in Europe (40-70% survival rate)[17,18] and in the United States (92%).[19] The purpose of this study is to describe a regional center use of hydroxocobalamin for inhalation injury and characterize the risk of mesenteric ischemia.

Methods

We conducted a retrospective analysis of all burn patients older than 18 who received hydroxocobalamin for suspected inhalation injury at a single burn center over a two-year period. Demographics and outcomes were recorded, including primary outcome of mesenteric ischemia or tube feed intolerance as a sign of enteric dysfunction. Additional secondary outcomes of mortality and vasopressor use were also tabulated. Inhalation injury was diagnosed by fiberoptic bronchoscopy, along with ABG with elevated carboxyhemoglobin, and clinical suspicion as adjunctive data points. Burn size, described in percent total body surface area (TBSA), abbreviated burn severity (ABSI) index, and grade of inhalation injury (0-4) were assessed. Fluid administration during resuscitation was also recorded for those with a burn size greater than or equal to 20% TBSA. Indications for hydroxcobalamin administration were elevated carboxyhemoglobin, bronchoscopy confirmation, and clinical suspicion for inhalation injury. Mesenteric ischemia was defined for this study as presence of pneumatosis or perforation on CT scan or necrotic bowel on laparotomy.

Results

Patient characteristics

From October 2015 to October 2017, twenty-one patients received hydroxocobalamin. Four were excluded from the study due to withdrawal of care for what was deemed to be a non-survivable injury. Of the remaining 17 cases, patients were primarily male (70.6%) with a median age of 60 years (45, 65 IQR) and a median ABSI score of 6 (5, 7 IQR) (*Table I*).

Injury characteristics and resuscitation

Four patients had isolated inhalation injuries without cutaneous burn injury. Of the thirteen patients with cutaneous and inhalation injury, TBSA had a median of 8.5% (1.8, 39 IQR) (*Table I*). Of the final sample of seventeen patients, nineteen percent of the patients who received hydroxocobalamin also received a formal fluid resuscitation for burn shock. The median fluid administration during resuscitation in the first 24 hours after injury was 3.1 (1.9, 4.4 IQR) (*Table I*).

Inhalation injury diagnosis and severity

Seventy-six percent (13 patients) received bronchoscopy. Fifty-three percent (9) were confirmed by carboxyhemoglobin. Bronchoscopy alone confirmed thirty-five percent (6). Carboxyhemoglobin alone confirmed eleven percent (2). Forty-one percent received both. Two patients received hydroxocobalamin due to clinical suspicion without carboxyhemoglobin testing or bronchoscopy (*Fig. 1*). Of the thirteen who received bronchoscopy, one case had grade 0, 15% (2) were grade 1, 30% (4) were grade 2, 15% (2) were grade 3, and 30% (4) were grade 4 inhalation injury (*Table I*).

Outcomes - mortality and mesenteric ischemia

Five percent (1 of 17) received vasopressors and that same patient (5%) suffered mortality related to renal failure and multisystem organ failure. This patient had 50% TBSA, grade 4 inhalation injury, and an ABSI score of 6. She developed abdominal compartment syndrome requiring decompressive laparotomy after large volume resuscitation and vasopressors. Under direct visualization, she had pink, healthy, peristaltic bowel without signs of mesenteric ischemia.

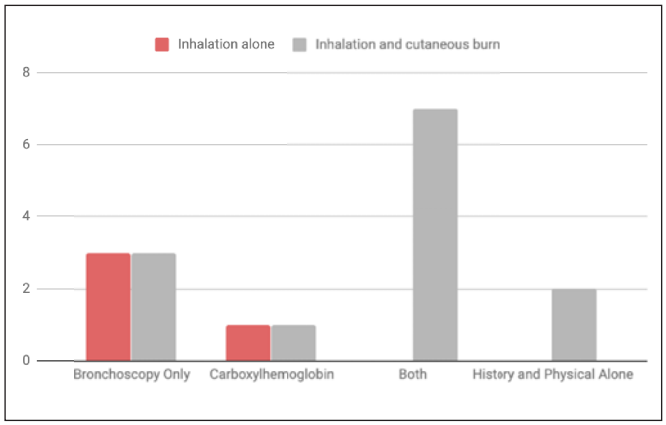

Fig. 1 - Method for inhalation burn confirmation

Table I - Demographics and injury characteristics

Characteristics	N (IQR)	Percent
Median age, y	60 (45, 65)	
Gender, n		
Male	12	70.60%
Female	5	29.40%
Fluid resuscitation cc/kg/hr in first 24 h, n	3.1 (1.9, 4.4)	
Median ABSI, n	6 (5, 7)	
TBSA		
Less than 1%	2	15%
1-9%	4	30%
10-19%	2	15%
20-29%	1	8%
30-39%	2	15%
40-49%	0	0%
50-59%	1	8%
60-69%	1	8%
Inhalation injury, n		
Grade 0	1	8%
Grade 1	2	15%
Grade 2	4	30%
Grade 3	2	15%
Grade 4	4	30%
Vasopressor use	1	5%
CRRT use	1	5%
Mortality	1	5%
AMI	0	0%

ABSI = abbreviated burn severity index; TBSA = total body surface area; CRRT = continuous renal replacement therapy; AMI = acute mesenteric ischemia

None of the patients developed tube feed intolerance or symptoms that necessitated imaging to evaluate for mesenteric ischemia. In addition, none of the surviving patients developed AKI regarding dialysis.

Discussion

The current retrospective study suggests that hydroxocobalamin administration for patients with smoke inhalation injury (with or without cutaneous burns) is not necessarily associated with mesenteric ischemia, in contrast to what was presented by Soussi et al.[3] Seventeen patients received hydroxocobalamin after their injury and none of them had tube feeding intolerance, had ever received a CT that showed signs of mesenteric ischemia, or had ischemic bowel during laparotomy. Furthermore, only one patient in this cohort required vasopressor use and that patient suffered mortality without developing mesenteric ischemia. With such a sharp contrast in data, the authors propose that there was something inherently different about the severity of illness and their clinical course in some of the French patients - which is supported by the higher median burn size (mean of 55%) and ABSI in their study. The fact that they received hydroxocobalamin was likely just a marker of how severe their injury was and how sick they were perceived to be. This premise is supported by the fact that hydroxocobalamin fell out as a risk

factor in their multivariate analysis, suggesting that hydroxocobalamin may be the "egg" and severity of illness is the "chicken" in this scenario.

They postulate the mechanism of hydroxocobalamin increasing risk of AMI may be due to splanchnic microvasculature vasoconstriction.[2] Of note, 66% of the patients in the AMI group received norepinephrine in the first twenty-four hours after burn injury. Additionally, thirteen percent of the AMI patients received dopamine within the first 24 hours. These patients also received higher doses of vasopressors than the control group.

Furthermore, only low cardiac output and early multiorgan dysfunction were independently related to a high risk of non-occlusive AMI. Interestingly, the AMI group received a higher amount of fluid resuscitation/kg than the control group yet continued to have lower cardiac index and higher multiorgan system failure scores. Furthermore, there was also no difference between the lowest mean arterial pressures between the two groups, which may be a result of vasopressor parameters instead of fluid or cardiac status. Taking the amalgamated data of the two studies in context, we suspect the mesenteric ischemia seen in the French study was related to critical illness and vasopressor use.

Although it is outside of what is presented in the current manuscript, the authors commonly treated AMI in the burn ICU. However, AMI has essentially disappeared in our practice since we have started restricting fluid administration, avoiding oversedation (less vasopressors), excising earlier, initiating earlier postpyloric feeds, improving standards of infection control, and minimizing cytotoxic wound agents. Although the severity of illness of survivors continues to increase, the overall course and trajectory of patients seems to improve each year.

Nguyen et al.[20] compared patients who received hydroxocobalamin to those with no antidotal intervention. They reported an association with lower pneumonia rates, fewer ventilator days, and increased ventilator free days. There was a trend toward lower hospital length of stay in the hydroxocobalamin group. Although there were unmeasured confounders that had the potential to affect results, the authors recommend that providers consider the empiric use of hydroxocobalamin in suspected smoke inhalation patients.

Hydroxocobalamin has treated vasopressor refractory hypotension in the setting of cardiopulmonary bypass[21-23] and liver transplant vasoplegic syndrome.[24] There was an immediate response to hydroxocobalamin with lasting improvement of blood pressure that decreased the use of vasopressor support without report of AMI.[25] Shock and/or low cardiac output result in a low flow mesenteric perfusion, which is worsened by heart failure and vasopressors[26] and when coupled with catecholamines released from burn injury can result in further vasospasm.[27]

Heavy fluid resuscitation after thermal injury potentially results in splanchnic congestion, which could also worsen hypoperfusion resulting in bacterial translocation and potential multi-organ system failure.[2] The shock state worsens, and intravascular hypovolemia develops, followed by hypotension and vasopressor use. This creates an ideal set up for multifactorial bowel ischemia, a component of vasoconstriction, venous congestion, and increased intra-abdominal pressure prevents bowel perfusion. Only 19% of our patients received a formal fluid resuscitation for burn shock with a median 3.1 (1.9, 4.4 IQR) cc/kg/%TBSA in the first 24 hours, in contrast to the French study where patients received 177% more fluid, with a median cc/kg/TBSA in the first 24 hours of 5.5 (3.4- 8.5). Our patients received a restrictive resuscitation, which included plasma administration and less overall fluid. This limited resuscitation could be related to why our patients had a lower mortality rate (5% vs. 27%) and did not have any AMI (0% vs. 5.5%). Additionally, Soussi[3] commented that the AMI group received 1.5x higher fluid volume in the first 24 hours than the control.

Limitations of our study are important to note. This was a retrospective study at a single center with limited cases, relatively small burn size, and less critical illness. We are unable to delineate concrete conclusions of causal relationships due to the observational design of the study. The small sample size might increase the chances of us assuming as true a false premise. Patients with non-survivable injuries who elected to have withdrawal of care were excluded from the study and thus we were unable to assess if they had AMI. We did not perform a CT scan, abdominal operation, or endoscopy on all of the patients studied to definitely

prove there was no low-grade AMI. Finally, the burn size was much smaller in this study than in the Soussi study,[3] making our patients much less predisposed to mesenteric ischemia. However, outside of this review, the authors have not seen a case of mesenteric ischemia in their burn center over a 4-year period, with approximately 350 admissions per year.

In summary, this study shows that hydroxocobalamin can be administered to a subset of patients without inducing mesenteric ischemia. Further multicenter study is necessary to definitively elucidate or disprove a relationship between hydroxocobalamin and mesenteric ischemia.

Conclusion

Hydroxocobalamin was not associated with mesenteric ischemia or even development of tube feed intolerance. This morbidity is in sharp contrast to the previously published data in which 5% of burn patients developed mesenteric ischemia. Differences may be due to patient severity of injury/illness, vasopressor use, or other unmeasured confounders in clinical course. Additional large-scale prospective studies should be conducted in the future to better delineate the role of hydroxocobalamin in treating inhalation injury.

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Appendix. Of the four patients who received formal fluid resuscitation, the resuscitation values were: 1.83, 2.58, 3.75, and 4.72 cc/kg/TBSA.
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