Compounded Cerium Nitrate—Silver Sulfadiazine Cream is Safe and Effective for the Treatment of Burn Wounds: A Burn Center's Four-Year Experience

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Abstract

Wound infections and sepsis are significant causes of morbidity after burn injury and can be alleviated by early excision and grafting. In situations that preclude early surgery, topical agents allow for a safer delay. Cerium nitrate compounded with silver sulfadiazine (Ce-SSD) is a burn cream that provides broad antibacterial activity, forms a temporary barrier, and promotes re-epithelialization. Methemoglobinemia is a rare, but oft-cited, systemic complication of Ce-SSD. In this retrospective review, 157 patients treated with Ce-SSD between July 2014 - July 2018 were identified and the monitoring protocol for methemoglobinemia during Ce-SSD treatment was evaluated. Median age was 59 years (IQR, 47-70.5 years), with total body surface area burn (TBSA) of 8.5% (IQR, 3-27), adjusted Baux score of 76 (IQR, 59-94), and inhalation injury present in 9.9% of patients. Primary endpoints included incidence of symptomatic and asymptomatic methemoglobinemia. Of the 9.6% (n = 15) of patients with methemoglobinemia, 73.3% (n=11) had maximum methemoglobin levels ≥ 72 hours from time of first application. One patient developed clinically significant methemoglobinemia. Patients with TBSA ≥ 20% were more likely to develop methemoglobinemia (OR 9.318, 95% CI 2.078 to 65.73, p = 0.0078), however neither Ce-SSD doses nor days of exposure were significant predictors. Ce-SSD application to temporize burn wounds until excision and grafting is safe, effective, and, in asymptomatic patients with TBSA < 20%, can be used without serial blood gas monitoring. Vigilant monitoring for symptoms should be performed in patients with TBSA ≥ 20%, but routine blood gases are not necessary.

Key Words: Cerium nitrate, Cerous nitrate, Silver sulfadiazine, Topical burn therapy, Methemoglobinemia, COVID-19, SARS-CoV-2

Introduction

Wound infection and sepsis are prominent causes of morbidity and mortality after burn injury. Despite the benefits of early excision and grafting(1-3), certain situations preclude early surgical management. These include patient inability to tolerate anesthesia, lack of suitable skin coverage material, and burns sustained in battle and mass casualty events, among others(2). To address these limitations, topical antimicrobial agents for burn wound management have been employed with varying success and side-effect profiles(4-7).

The rare-earth element cerium, an inexpensive and nontoxic metal, has historically been used in its cerium salt form as a topical burn treatment due to its broad antibacterial activity and poor systemic absorption(8). Likewise, silver sulfadiazine has been used as a topical treatment due to the antimicrobial activity of silver ions after dissociation(9). In 1976, a combination of the two was first introduced and reported to have superior antimicrobial activity than either substance alone(10). This enhanced activity against gram-negative bacteria, gram-positive bacteria, and fungi(11) has been attributed to Ce-SSD's ability to bind and neutralize the immunosuppressive lipid protein complex (LPC) that is created in and around burned tissue(2, 12). Ce-SSD treated areas develop a tough, leathery eschar that acts as an occlusive layer, promoting a moist wound healing environment and preventing bacterial invasion(2). Recent findings by Qian *et al.* suggest that cerium nitrate improves the quality of burn eschar via attenuation of burn-induced DAMPs, tissue inflammatory responses, and regrowth of resident skin flora(20). In addition, Ce-SSD is purported to have a local effect on calcium homeostasis, altering extracellular calcium concentrations in the wound bed, and ultimately playing a role in keratinocyte proliferation, maturation, and re-epithelialization(2, 8). Previous

studies have provided evidence of a synergistic relationship between silver and cerium, yielding a superior topical agent in the treatment of burns. A study of 853 patients with burns treated with Flammacerium (cerium nitrate-silver sulphadizine) and staged surgery by Scholten-Jaegers *et al.* found a lower overall mortality rate and fewer instances of sepsis and septic shock in comparison with the literature(21).

Methemoglobinemia (MetHba) is a commonly cited, but rarely occurring, systemic complication of Ce-SSD(13). Clinical consequences are dependent on the degree of MetHba, and range from headache and cyanosis to cardiac ischemia, hypotension, and even death(14). A previously published retrospective review by Kath *et al.* examined 170 patients between 2005-2009 and found a 10% incidence of MetHba, with only 2% of those patients developing symptomatic MetHba(15). The authors concluded that morbidity and mortality from Ce-SSD-induced MetHba can be decreased via early diagnosis and vigilant monitoring(15). Subsequently, this institution enacted a screening protocol to monitor Methemoglobin (MetHb) in Ce-SSD-treated burns via serial ABGs drawn before Ce-SSD application, at 24 hours after Ce-SSD application, and at 72 hours after Ce-SSD application. This retrospective cohort study adds to the findings of Kath *et al.* by assessing the utility of the screening protocol and further characterizing the toxicity of Ce-SSD(15). We hypothesize that days exposed to Ce-SSD, doses of Ce-SSD, and %TBSA will be the main determinants for developing MetHba.

Methods

Patient Population

Following local institutional review board approval, medical and pharmacy records were queried for all patients admitted to a regional burn center between July 2014 and July 2018 who had Ce-SSD-treated burns. Data including demographics,

admission/discharge information, mechanism of injury and management, symptoms, complications, timing of Ce-SSD administration, surgical information, laboratory values, and methemoglobin trends were extracted. Primary endpoints included incidence and management of MetHba. Physiologic levels of MetHb are dynamic and range from 0-3%[17], therefore MetHb greater than 3.0% was defined as MetHba.

Ce-SSD Formulation and Application

Ce-SSD is prepared by compounding 22mL of 100% $Ce(NO_3)_3$ filtered stock solution with 1,000g of SSD cream. Typically, the Ce-SSD cream is kneaded into the matrix of a standard dry dressing and applied twice daily to a patient's burn wound(15).

Statistical Analysis

Statistical analyses were performed using Prism 8 (GraphPad Software Inc., La Jolla, CA). Descriptive statistics were used to summarize the distributions and proportions of study variables. Analysis of continuous variables was performed using the Wilcoxon rank sum test and categorical variables analyzed via the X^2 or Fisher's exact test, as appropriate, with a p-value < 0.05 considered statistically significant. Receiver-operating characteristic (ROC) curves were generated for continuous variables to determine sensitivity and specificity for predicting MetHba. A sensitivity of 100% was preferred for screening protocol and Youden Index ($J = \max \{Se(c) + Sp(c) - 1\}$) was used to determine optimal cut-offs, where applicable. $p < 0.05$ was considered statistically significant. Simple logistic regression modeling was used to determine the ability of selected variables to predict MetHba and an adjusted model, selected using Akaike's Information Criterion, was created using multivariate logistic regression modeling.

Results

One hundred and fifty-seven patients had burn injuries that were treated with Ce-SSD. Table 1 summarizes patient demographics and Table 2 summarizes clinical information. The median age was 59 years (IQR, 47 – 70.5 years), with most patients identifying as African American (47.1%) and male (65.6%). Burn etiologies were predominantly flame (47.8%), and median total body surface area (TBSA) burn was 8.5% (IQR, 3-27), with 9.9% of patients suffering an inhalation injury. The median Modified Baux Score was 76 (IQR, 59-94) and mortality was 16.6% (n = 26). Figure 1 shows %TBSA vs. Age in patients with a Modified Baux Score < 100 who did not survive their burn injury.

Median MetHb before Ce-SSD application was 1.2% (IQR, 0.8-1.4), while measurements at first and second screenings were 1.2% (IQR, 0.9-1.5) and 1.4% (IQR, 1-1.8), respectively. There was good adherence to the protocol, with 1st and 2nd ABGs drawn at 22.7 hours (IQR, 15.2-26.9 hours) and 70.8 hours (IQR, 61.9-74.4 hours) after Ce-SSD application, respectively, although 17.2% (n = 27) of the time there was no MetHb measurement prior to Ce-SSD application. One hundred thirty-one patients had a maximum MetHb level between 0 and 3.0%, while 15 patients had a MetHb level above 3.0%. Figure 2 details the average %MetHb over time after Ce-SSD application in patients who developed MetHba. Maximum MetHb occurred within 72 hours of initial Ce-SSD application in 67.1% (n = 98) of patients, while MetHba was found in 9.6% (n = 15) of patients. However, only 4 patients who developed MetHba did so within 72 hours of initial Ce-SSD application, while 11 (73.3%) developed MetHba after 72 hours. Of the patients who had late

development of MetHba, only 2 (18.2%) had a Ce-SSD exposure less than 72 hours, while all others were treated with Ce-SSD for > 3 days.

Flame injury accounted for 93.3% (n = 14) of patients with MetHba. Patients with MetHba had larger median %TBSA (47% vs 7.5%, $p < 0.0001$), a higher incidence of inhalation injury (33.3% vs 7.8%, $p = 0.0308$), higher mortality (40% vs 14.1%, $p = 0.0102$), a higher median Modified Baux Score (106 vs 72.5, $p < 0.0001$), received more total doses of Ce-SSD (30 vs 7, $p = 0.0049$), had higher MetHb at 1st screening (1.5% vs 1.2%, $p = 0.0019$) and 2nd screening (2.1% vs 1.3%, $p < 0.0001$), and had longer exposure to Ce-SSD overall (5.7 days vs 1.3 days, $p < 0.0001$) (Table 2).

Twenty-six deaths were noted in this study, 20 in the non-MetHba group and 6 in the MetHba group. Four patients within this review were treated with Methylene Blue. The indication for treatment in three of these patients was refractory vasoplegia, not hypoxia or symptomatic MetHba, despite two of these patients having MetHb levels of 3.1% and 4.8%. All three of these patients died. One patient (6.7% of patients with MetHba and 0.6% of all patients) developed symptomatic MetHba and was found to have a MetHb level of 9.4% (increased from MetHb of 1.8% the day prior). This patient required reintubation for hypoxia, was treated with Methylene Blue for symptomatic MetHba, and survived.

ROC curves generated for continuous variables to determine sensitivity and specificity for predicting MetHba generated optimal cut-offs of > 19.75% TBSA, > 29.5 Ce-SSD doses, and > 4.193 Ce-SSD days (Figure 3). The area under the ROC curve (AUC), p value, sensitivity (SN), and specificity (SP) for each of these variables and optimal cut-offs were as follows: %TBSA AUC = 0.91, $p < 0.0001$; %TBSA > 19.75% SN = 86.7%, SP = 71.9%. Ce-SSD doses AUC = 0.72, p =

0.0057; Ce-SSD doses > 29.5 SN = 53.3%, SP = 87.3%. Ce-SSD days AUC = 0.76, p = 0.0008; Ce-SSD days > 4.193 SN = 60%, SP = 82.4%. In order to confer practical application in the clinical setting, cut-offs of ≥ 20% TBSA, ≥ 30 Ce-SSD doses, and ≥ 4 Ce-SSD days were used in the analysis. Univariate modeling via simple logistic regression (Table 3) demonstrated a significant increase in likelihood of MetHba in flame injured patients (OR 18.6, 95% CI 3.6 to 341.3, p = 0.0053), TBSA ≥ 20% (OR 17.8, 95% CI 4.6 to 117.2, p = 0.0002), presence of inhalation injury (OR 4.8, 95% CI 1.2 to 17.2, p = 0.0192), increasing Modified Baux Score (OR 1.1, 95% CI 1.0 to 1.1, p < 0.0001), Ce-SSD Doses ≥ 30 (OR 7.9, 95% CI 2.5 to 25.1, p = 0.0003), and Ce-SSD Exposure ≥ 4 days (OR 6.7, 95% CI 2.2 to 21.6, p = 0.0009). The adjusted model created using multivariate logistic regression (Table 3; Figure 3) demonstrated that only TBSA ≥ 20% led to a significant increase in likelihood of MetHba (OR 9.3, 95% CI 2.08 to 65.7, p = 0.0078). In the adjusted model < 20% vs ≥ 20% TBSA had an AUC = 0.86, p < 0.0001 with a negative predictive power of 92.8% and a positive predictive power of 80%.

Discussion

Ce-SSD, a combination ointment consisting of cerium nitrate and silver sulfadiazine, is widely used in Europe under the trade name Flammacerium and has been shown to increase the rate of healing up to 2.2-fold in large or massive burns(18). Despite the positive effect on wound healing and evidence of decreased wound infections, Ce-SSD is used sparingly in the United States due to the rare, but commonly cited, side effect of symptomatic methemoglobinemia. At this institution, Ce-SSD is frequently used as a topical antimicrobial, as well as for temporization of burn wounds prior to tangential excision, and is generally well-tolerated. A previously

published retrospective 5-year review by this group found a low incidence of MetHba secondary to Ce-SSD treatment of burn wounds. Only 10% of Ce-SSD-treated patients developed MetHba, as defined as above laboratory reference range, with an even smaller proportion (2%) developing clinically significant levels. The conclusion at that time was that morbidity and mortality from Ce-SSD-induced MetHba could be decreased via early diagnosis and vigilant monitoring(15), allowing for timely intervention (such as Ce-SSD cessation or administration of methylene blue), to prevent the potentially serious consequences of MetHba. A screening protocol to monitor MetHb in Ce-SSD-treated burns via serial ABGs was therefore established.

While this study again confirms the low incidence of clinically significant MetHba in Ce-SSD-treated burns, MetHba was most often detected in patients treated with Ce-SSD for greater than 72 hours. For this reason, early serial ABG monitoring is not necessarily helpful in preventing clinically significant MetHba due to Ce-SSD. Additionally, the single patient that was suspected of having symptomatic MetHba also had several confounding factors that contributed to hypoxia, making the true incidence of clinical hypoxia from MetHba alone unclear. Ultimately, routine education on the side-effect profile of Ce-SSD for all involved providers and vigilance on the part of care team have become the standard of care at this institution.

The need for a safe alternative to early excision and grafting in thermally injured patients has never been more apparent than it is now in the era of COVID-19. The COVID-19 pandemic has impacted patients, providers, and standard practices of hospitals around the world. The typical insult to a burn patient's respiratory tract due to inhalation injury, inflammatory mediators associated with infection, sepsis, or the burn wound itself (19) has been further compounded by the respiratory sequelae of COVID-19. Prevention of burn wound infection and sepsis when patients cannot

safely undergo operative intervention is critical, and the use of Ce-SSD offers a safe option that requires no additional monitoring by providers. This group's experience with COVID-19 and thermally injured patients has reinforced this practice, as we believe it has minimized the additional insult to the respiratory tract that can come from an unprotected burn wound. The potential to minimize surgical intervention in periods after mass casualties, natural disasters, and other resource limited scenarios is significant.

This study is limited as a retrospective chart review from a single institution. Additionally, the absence of wound and blood culture data limits further analysis based on different pathogenic organisms which may affect our results. However, burn wound cultures are not routinely obtained at this institution. While MetHb levels were acquired relatively early in the hospital course, other previously administered medications, such as copper supplementation or anesthetic agents, might have impacted the MetHb levels. Note that while both genetic abnormalities and nitrite ingestion can lead to methemoglobinemia, no patients in this cohort had known elevated levels prior to their Ce-SSD administration.

Conclusion

At this institution, a screening protocol for Methemoglobinemia was successfully implemented, and demonstrated an extremely low incidence of both asymptomatic and symptomatic MetHba in patients being treated with Ce-SSD. Given this data, monitoring for MetHba is not necessary in patients with a TBSA < 20%; in patients with a TBSA > 20%, clinical vigilance is important, but serial laboratory data can be avoided. This study supports that Ce-SSD can be safely used to temporize burn wound excision and grafting without the need for routine monitoring for MetHba.

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Figure Legends

Figure 1. %TBSA vs. Age in patients with a Modified Baux Score < 100 who did not survive burn injury.

Figure 2. Average %MetHb over time after Ce-SSD application in patients who developed MetHba.

Figure 3. Receiver-operating characteristic curves of %TBSA, Ce-SSD Doses, Ce-SSD Days, and Adjusted Model < 20% vs ≥ 20% TBSA depicting ability to discriminate between MetHb ≤ 3.0% and MetHb > 3.0%. Youden Index (J = max {Se (c) + Sp (c) − 1}) was used to determine optimal cut-off, where applicable. $p < 0.05$ was considered statistically significant. A sensitivity of 100% was preferred for screening protocol. Area under the curve (AUC), p-value, cut-off values, Negative predictive power, and Positive predictive power (where applicable) are as follows:

%TBSA: AUC = 0.9104, $p < 0.0001$; Cut-off > 17.5% TBSA (100% Sensitivity, 66.67% Specificity); Cut-off > 19.75% TBSA (86.67% Sensitivity, 71.85% Specificity); Cut-off > 21.00% TBSA (86.67% Sensitivity, 72.59% Specificity); Cut-off > 61.63% TBSA (26.67% Sensitivity, 100% Specificity).

Ce-SSD Days: AUC = 0.7629, $p = 0.0008$; Cut-off > 0.9354 Ce-SSD Days (100% Sensitivity, 33.1% Specificity); Cut-off > 3.908 Ce-SSD Days (60% Sensitivity,

81.69% Specificity); Cut-off > 4.193 Ce-SSD Days (60% Sensitivity, 82.39% Specificity); Cut-off > 20.23 Ce-SSD Days (13.33% Sensitivity, 100% Specificity).

Ce-SSD Doses: AUC = 0.7174, p = 0.0057; Cut-off > 2.5 Ce-SSD Doses (100% Sensitivity, 11.97% Specificity); Cut-off > 29.5 Ce-SSD Doses (53.33% Sensitivity, 87.32% Specificity); Cut-off > 92.5 Ce-SSD Doses (20% Sensitivity, 100% Specificity).

Adjusted Model < 20% vs ≥ 20% TBSA: AUC = 0.8638, p < 0.0001, Negative predictive power = 92.76%, Positive predictive power = 80.00%.

Table 1. Demographics and comparison of patients with and without methemoglobinemia.				
Demographics	All Patients (n= 157)	No MetHba (n = 142)	MetHba (n = 15)	p-value [a]
Age (years)	59 (47-70.5)	59 (47-71)	56 (51-70)	0.9423
Gender: Male, % (No.)	65.6% (n = 103)	66.9% (n = 95)	53.3% (n = 8)	0.2928
Race/Ethnicity				0.5455
African American	47.1% (n = 74)	45.8% (n = 65)	60% (n = 9)	-
Caucasian	40.8% (n = 64)	41.6% (n = 59)	33.3% (n = 5)	-
Hispanic	12.1% (n = 19)	12.7% (n = 18)	6.7% (n = 1)	-
Mechanism of Injury				**0.0002**
Flame	47.8% (n = 75)	43% (n = 61)	93.3% (n = 14)	-
Non-Flame	52.2% (n = 82)	57% (n = 81)	6.7% (n = 1)	-
Tobacco use [b]	15.3% (n = 24)	13.4% (n = 19)	33.3% (n = 5)	0.0564
%TBSA	8.5 (3-27)	7.5 (3-22.5)	47 (32-62.5)	**< 0.0001**
Inhalation Injury [c]	9.9% (n = 14)	7.8% (n = 10)	33.3% (n = 4)	**0.0308**
Mortality	16.6% (n = 26)	14.1% (n = 20)	40% (n = 6)	**0.0102**

Data presented as median and interquartile range (IQR) or % (n), where appropriate. p-values calculated with the use of a X^2 or Fisher's exact test or Mann-Whitney U test; $p < 0.05$ considered statistically significant.

Abbreviations: MetHba = Methemoglobinemia; No. = number; TBSA = Total Body Surface Area.

[a] No MetHba vs MetHba.

[b] +Tobacco vs - Tobacco and Unknown/Not Documented.

[c] +Inhalation Injury vs -Inhalation Injury and Unknown/Not Documented.

Table 2. Comparison of clinical information.				
	All Patients (n = 157)	No MetHba (n = 142)	MetHba (n = 15)	p-value [a]
Modified Baux Score	76 (59-94)	72.5 (55-89.5)	106 (93-122.5)	**< 0.0001**
Total Doses Ce-SSD	8 (4-21.5)	7 (4-20.25)	30 (6-70)	**0.0049**
Pre Ce-SSD MetHb (%)	1.2 (0.8-1.425)	1.2 (0.8-1.4)	1.2 (0.8-1.5)	0.8015
MetHb (%) at 1st Screening	1.2 (0.9-1.5)	1.2 (0.9-1.425)	1.5 (1.35-2.25)	**0.0019**
MetHb (%) at 2nd Screening	1.4 (1-1.8)	1.3 (1-1.575)	2.1 (1.5-3.7)	**< 0.0001**
Days of Exposure to Ce-SSD prior to maximum MetHb	1.713 (0.5729-3.384)	1.358 (0.5028-3.09)	5.675 (1.675-10.63)	**< 0.0001**
Symptomatic MetHba	0.64% (n = 1)	0% (n = 0)	6.67% (n = 1)	0.0955

Data presented as median and interquartile range (IQR) or % (n), where appropriate. p-values calculated with the use of a X^2 or Fisher's exact test or Mann-Whitney U test; $p < 0.05$ considered statistically significant.

Abbreviations: MetHba = Methemoglobinemia; MetHb = Methemoglobin; Ce-SSD = Cerium Nitrate—Silver Sulfadiazine.

[a] No MetHba vs MetHba

Table 3. Likelihood of methemoglobinemia.			
Univariate models	OR	95% CI	p-value
Flame Injury	18.59	3.587 -341.3	**0.0053**
%TBSA	1.104	1.064 - 1.157	**< 0.0001**
< 20% vs ≥ 20% TBSA	17.79	4.639 -117.2	**0.0002**
Inhalation Injury	4.800	1.171 - 17.19	**0.0192**
Modified Baux Score	1.079	1.045 -1.124	**< 0.0001**
Total Doses Ce-SSD	1.032	1.015 - 1.054	**0.001**
< 30 vs ≥ 30 Ce-SSD Doses	7.873	2.544 - 25.11	**0.0003**
Days of Exposure to Ce-SSD prior to maximum MetHb	1.245	1.105 - 1.426	**0.0006**
< 4 vs ≥ 4 Days Ce-SSD Exposure	6.692	2.223 - 21.56	**0.0009**
Adjusted model: Adjusted for %TBSA, Total Doses Ce-SSD, and Days of Exposure to Ce-SSD prior to maximum MetHb.			
< 20% vs ≥ 20% TBSA	9.318	2.078 - 65.73	**0.0078**
< 30 vs ≥ 30 Ce-SSD Doses	1.615	0.3810 - 6.470	0.5016
< 4 vs ≥ 4 Days Ce-SSD Exposure	1.951	0.4692 - 7.950	0.3472
p < 0.05 considered statistically significant. Abbreviations: OR = Odds Ratio; 95% CI = 95% Confidence Interval; TBSA = Total Body Surface Area; Ce-SSD = Cerium Nitrate—Silver Sulfadiazine; MetHb = Methemoglobin.			

Figure 1

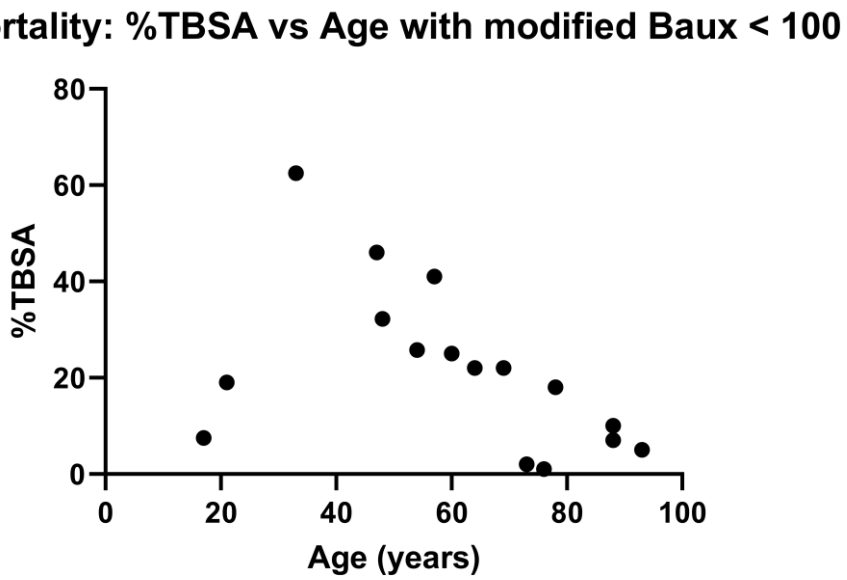

Figure 2

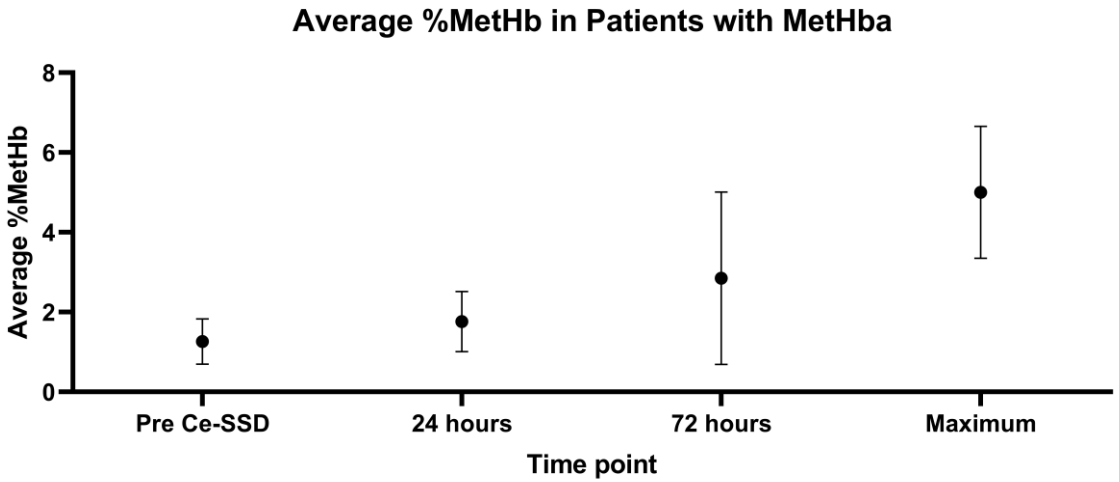

Figure 3