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The Kitchen Sink: Mortality Assessment of Salvage Therapies in Refractory Shock

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Abstract

Objective: The management of refractory shock remains a challenge with nearly ubiquitous mortality requiring novel therapies to maintain hemodynamics when conventional mechanisms fail. Several exploratory therapies display potential efficacy in the literature, but it remains unclear which therapy is superior. We aim to clarify the efficacy of the current salvage therapies: Angiotensin II (ATII) vs Methylene Blue (MB) vs Vitamin C with thiamine and hydrocortisone (VC) for refractory shock. We hypothesize that these therapies will improve survivability and decrease other vasopressors in patients with refractory shock.

Design: Retrospective chart review.

Setting: Single center mixed intensive care unit (ICU).

Patients: Adult patients admitted to the ICU with refractory shock between January 2015 through September 2018.

Interventions: Initiation of ATII, MB, and/or VC.

Measurements: The primary outcome was in hospital mortality. Secondary outcomes included: change in dosage of standard vasopressors after initiation of salvage therapy, incidence of acute renal failure (ARF) with need for renal replacement therapy (RRT), and ICU length of stay.

Results: As monotherapy, those that received ATII (34 patients), mortality was seen in 85.3%, for MB, 77.8%, and for Vit C, 51.9%. After adjusting for severity of illness, those who received ATII alone as compared to VC had a significant higher mortality (aOR=3.45; 95% CI=confidence interval: 1.08–10.99; P=0.036) vs (OR=0.36; 95% CI: 0.19–0.67; p=0.001), respectively. No statistical difference was seen in norepinephrine equivalents after initiation of salvage therapy. ATII groups did have a significantly higher incidence of RRT.

Conclusion: While these therapies have shown improvement in hemodynamics in recent literature, this study questions the impact on overall mortality. This could be due to the baseline low survivability in this patient population and not initiating these rescue therapies soon enough. More prospective studies are needed to further clarify their potential role in refractory shock.

Keywords

Shock, Hemodynamics, Angiotensin II, Methylene Blue, Ascorbic Acid, Vasoconstrictor Agents

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Introduction

Mortality associated with shock is significant, dictated by a circulatory collapse unresponsive to conventional therapy which leads to insufficient tissue oxygenation and ultimately multisystem organ failure [1]. Distributive shock remains the most common shock state and its management is driven by monitoring end organ perfusion markers while ensuring adequate volume resuscitation and vasopressor infusions as necessary [2]. Catecholamines and vasopressin-like peptides are the two main types of vasopressors used for shock, and high doses of these medications are often required for profoundly vasoplegic states [3,4]. Refractory shock is dictated by inadequate hemodynamic response despite high doses of vasopressor medications. [5-25] The management of catecholamine and vasopressor resistant shock is a clinical challenge, often forcing the provider to introduce third line therapies as the mortality associated with refractory shock exceeds 50% [5].

Salvage therapies born out of necessity to treat severe shock states have shown potential efficacy in medical literature. [25] Angiotensin-2 (AT II), a naturally occurring hormone of the renin angiotensin system causes direct vasoconstriction of both arteries and veins and was able to significantly reduce catecholamine and vasopressor doses compared to placebo when used in refractory shock states, thus making it a new contender in the vasopressor arena [3,5]. Methylene blue (MB) was initially shown as a treatment for refractory anaphylactic shock as it selectively inhibits the nitric oxide-cGMP pathway and thus inhibiting smooth muscle relaxation. This treatment strategy was extended to refractory distributive shock as case reports and small clinical trials demonstrated a significant vasopressor reduction with the addition of MB [6-12]. Glucocorticoids have been used in the treatment of septic shock for decades, although the mortality benefit is not clearly defined [13-15]. Clinical experimentation with the combination of hydrocortisone with synergistic agents including Vitamin C and thiamine (VC), have shown potentially positive results in severe sepsis [16-18]. Of note, these were relatively small studies and a recent randomized control trial did not show improvement in days alive or vasopressor independence when comparing VC to hydrocortisone alone [19] . Additionally, recent studies on vitamin C in sepsis in acute lung injury have had controversial results without benefit in organ dysfunction scores [20].

Each of the therapies listed has demonstrated hemodynamic improvement in the treatment of shock due to severe sepsis, each taking advantage of different mechanisms responsible for vasoplegia. There have been no studies to date comparing the efficacy of each therapy as compared to one another. This retrospective review was designed to analyze those patients which remained hypotensive despite maximum therapy with conventional vasopressors. The primary outcome was in hospital mortality in this group of patients. Secondary outcomes included change in Mean Arterial Pressure as compared to norepinephrine equivalents (MAP/NEE), intensive care unit (ICU) length of stay, and occurrence of new renal replacement therapy.

Materials and Methods

Study Design and Participants

The assessment was performed utilizing an IRB-approved

retrospective review of patients with refractory shock in a single center mixed ICU composed of medical, surgical, and neurological patients between January 2015 and September 2018. Inclusion criteria included patients who were age 18 or older, were admitted to the ICU, and started on salvage therapies, specifically angiotensin II, methylene blue, and/or vitamin C with thiamine and hydrocortisone. We defined this population as having refractory shock because these salvage therapies were not utilized until at least two or more of these standard vasopressors were used: norepinephrine, vasopressin, epinephrine, and/or phenylephrine. The use of salvage therapies was driven by the continued need for further hemodynamic support per clinical judgment of the treating attending physician. We collected baseline demographics on all patients, including: age, sex, race, BMI, APACHE II, SOFA, shock etiology, operative interventions, need for circulatory support, lactate levels, MAPs and NEE dosages at serial time points, as well as complications, including: renal failure, need for renal replacement therapy, venous thromboembolism, acute respiratory distress syndrome, and use of nitric oxide, or prostacyclin.

Outcomes Measured

The primary outcome measured was mortality during hospitalization. Secondary outcomes assessed during hospitalization to discharge included: MAP/NEE ratios at time intervals relative to initiation of therapy (-1h, 0h, 1h, 3h, 6h, 12h, 24h), incidence of acute renal failure with need for renal replacement therapy, and ICU length of stay. Norepinephrine equivalents were calculated to determine the standard dose of vasopressors [21].

Statistical Analysis

Demographic and clinical characteristics were compared between salvage therapy treatment groups at the univariate level. ANOVA and the Kruskal-Wallis test were used for normally distributed and nonparametric continuous variable comparisons, respectively. Chi-Square and Fisher's exact test were used for categorical variable comparisons with adequate and low cell counts, respectively. Outcomes of interest were similarly compared at the univariate level by way of the aforementioned tests. Continuous outcomes were analyzed for skewness and kurtosis, where positively-skewed outcomes were natural logarithm (ln) transformed to better meet the assumptions for generalized linear modeling (GLM) at the multivariable level. A subgroup analysis of septic and mixed shock only was performed.

Demographics and clinical characteristics with corresponding between-therapy univariate test comparison resulting in $P<0.2$ were adjusted for potential confounding covariates in multivariable analysis in order to better detect the independent association between therapy and outcome. Multivariable logistic regression modeling and GLM was used for categorical and continuous outcomes, respectively. Backward stepwise selection was used with $\alpha=0.1$ stay criteria in each model. Multicollinearity of covariates was assessed by way of variance inflation factor (VIF) analysis in conjunction with the condition index where VIF<2 was considered acceptable. SAS version 9.4 (SAS Institute Inc., Cary, NC) was used for all data analysis and two-sided test $P<0.05$ was considered statistically significant.

Results

From January 2015 to September 2018, 191 patients were identified to have received any or all of the salvage therapies of AT II, MB, and VC. (Table 1) Men accounted for 67% (n=129) of our cohort, and the average age was 60. Overall mortality amongst all groups as a whole was 65% (125/191). Thirty-four patients received AT II only, 9 patients received MB only, and 79 patients received VC only in addition to their standard vasopressors. We also identified those with mixed therapies. One patient received both AT II and MB,

Table 1: Baseline characteristics at or before initiation of salvage therapies.

Variable	AT II only (n=34)	MB only (n=9)	Vit C only (n=79)	AT II + Vit C (n=37)	MB + Vit C (n=27)	All 3 (n=4)	*P*
Age	59.5 ± 15.5	59.3 ± 14.3	62.2 ± 15.3	60.7 ± 13.2	56.7 ± 14.6	52.5 ± 5	0.2178
Female	9 (26.5)	3 (33.3)	31 (29.2)	12 (32.4)	6 (22.2)	0 (0)	0.2762
Race							0.2982
AA	18 (52.9)	4 (44.4)	50 (63.3)	22 (59.5)	19 (70.4)	3 (75.0)	
Asian/PI	2 (5.9)	-	2 (2.5)	1 (2.7)	-	-	
Caucasian	8 (23.5)	2 (22.2)	17 (21.5)	13 (35.1)	3 (11.1)	1 (25.0)	
Hispanic	2 (5.9)	-	-	-	-	-	
Other	4 (11.8)	3 (33.3)	10 (12.7)	1 (2.7)	5 (18.5)	-	
BMI	28.5 ± 8.9	26.7 ± 4.2	29.5 ± 10.9	33.2 ± 8.5	31.7 ± 11.9	23.0 ± 3.5	0.0158
APACHE	26.4 ± 7.8	26.7 ± 7.7	21.5 ± 8.1	24.9 ± 7.5	23.5 ± 7.7	24.5 ± 8.5	0.1109
SOFA	10.5 ± 3.4	11.1 ± 4.1	8.1 ± 3.2	10.6 ± 3.0	9.5 ± 3.3	10.3 ± 1.0	0.0006
Cause of Shock							0.0329
Cardiogenic	-	-	1 (1.3)	1 (2.7)	-	-	
Hemorrhagic	3 (8.8)	-	2 (2.5)	-	-	-	
Multifactorial	9 (26.5)	1 (11.1)	6 (7.6)	4 (10.8)	1 (3.7)	1 (25.0)	
Sepsis	22 (64.7)	8 (88.9)	70 (88.6)	32 (86.5)	26 (96.3)	3 (75.0)	
Mechanical Circulatory Support (VV/VA ECMO, VAD, Impella)	3 (8.8)	1 (11.1)	6 (7.6)	3 (8.1)	0 (0)	0 (0)	0.6456
Surgical Interventions	10 (29.4)	4 (44.4)	22 (27.9)	14 (37.8)	9 (33.3)	0 (0)	0.6943
VTE	1 (2.9)	0 (0)	3 (3.8)	0 (0)	0 (0)	0 (0)	0.7579
ARDS	15 (44.1)	3 (33.3)	15 (19.0)	15 (40.5)	12 (44.4)	4 (100.0)	0.0003
On Inhaled Prostacycline	11 (32.4)	0 (0)	7 (8.9)	16 (43.2)	5 (18.5)	2 (50.0)	0.0001
AKI	18 (52.9)	5 (55.6)	45 (57.0)	20 (54.1)	19 (70.4)	0 (0)	0.2065
RRT	10 (29.4)	2 (22.2)	16 (20.3)	8 (21.6)	4 (14.8)	0 (0)	0.8108
Lactate	7.5 ± 5.8	6.3 ± 4.9	5.6 ± 5.4	7.7 ± 5.5	8.2 ± 6.6	5.3 ± 1.6	0.0909
MAP at initiation	66.4 ± 11.2	76.1 ± 19.8	73.0 ± 12.7	76.3 ± 16.3	69.3 ± 13.5	78.5 ± 16.3	0.0722
Norepinephrine Equivalents at initiation	62.8 ± 26.9	57.5 ± 30.5	40.8 ± 24.3	61.1 ± 23.8	49.9 ± 24.1	63.0 ± 20.4	0.27

37 patients received AT II and VC, and 27 patients received MB and VC. Four patients were identified who received a combination of all three salvage therapies: AT II, MB, and VC. This is best visualized by the accompanying Venn diagram (See additional file 1). Their baseline characteristics differed in BMI, SOFA scores, etiology of shock (most due to sepsis), ARDS, and use of nitric oxide, or prostacyclines.

Primary Outcome

To assess the primary outcome of mortality, the individual and combination groups of salvage therapies were analyzed. When looking at the individual salvage drug groups, the AT II only group had a mortality of 85.3% (29/34 patients), MB group had a mortality of 77.8% (7/9 patients), and VC group had the lowest mortality of 51.9% (41/79 patients) which was statistically significant (P=0.008). The combinations of AT II + MB had 0% mortality (0/1 patient), AT II + VC had 67.6% (25/37 patients), and MB + VC had 74.1% (20/27 patients). The patients who received all three salvage therapies had 75% mortality (3/4 patients)

After adjusting for baseline characteristics, AT II therapy alone had significantly higher odds of mortality relative to VC only (aOR=adjusted odds ratio=3.45; 95% CI=confidence interval: 1.08 – 10.99; P=0.036), whereas MB therapy alone was not detected significantly different from VC only in regards to mortality (aOR = 3.42; 95% CI: 0.62 – 18.85; P=0.158). VC only was used as reference due to the fact that it had the lowest mortality and highest sample size. The combination therapies did not show any statistical difference in mortality after adjusting for baseline characteristics (Table 2).

To identify the individual effect of each salvage medication, they were adjusted for the other therapies, but no statistical difference was seen. However, AT II and MB trended towards higher odds of mortality with aORs of 1.86 and 1.91, respectively (P=0.103 and P=0.118, respectively). After adjusting for baseline characteristics, no significant relation to mortality was identified with AT II (aOR=0.97; 95% CI: 0.40 - 2.35; P=0.953)), whereas MB still trended towards higher odds of mortality (aOR=1.83; 95% CI 0.73 - 4.57; P=0.197). Vitamin C trended towards lower odds of mortality relative to those who did not receive it (aOR 0.38; 95% CI: 0.14 – 1.04; P=0.06). The subgroup analysis of septic and mixed shock alone showed similar results with VC having the lowest mortality (OR 0.36 (0.19 - 0.67) p= 0.001). (Additional File 3)

Secondary Outcomes

Norepinephrine equivalents (NEE) were used to effectively compare a change in standard vasopressor dosage after initiation of salvage therapies. MAP/NEE ratio significantly increased over time for AT2, VC, and MB. (Figure 2, Additional File 2) The relationship between AT2 dosing and NEE is better shown in Figure 1.

In regards to acute renal failure requiring renal replacement therapy (RRT), the analysis included those patients not on RRT within 72 hours prior to initiation of salvage therapies and excluded those already receiving RRT. After initiation of salvage therapies, in the AT II only group, 9/17 patients (52.9%) required RRT. In the AT II + VC group, 12/24 patients (50%) started RRT whereas only 6/62 patients (9.7%) in the VC group and 2/21 patients (9.5%) in the MB + VC group required RRT. For groups with AT II, a statistically significant difference was seen for patients requiring RRT. (Table 3)

When assessing ICU length of stay, there was no statistically significant difference seen among the groups overall (P = 0.454) or via

Table 2: Unadjusted and Adjusted Mortality.

Outcomes	AT II only (n=34)	MB only (n=9)	Vit C only (n=79)	AT II + MB (n=1)	AT II + Vit C (n=37)	MB + Vit C (n=27)	All 3 (n=4)
Mortality *	29 (85.3)	7 (77.8)	41 (51.9)	0 (0)	25 (67.6)	20 (74.1)	3 (75.0)
Unadjusted OR (95% CI)	5.38 (1.89 – 15.31)	3.24 (0.63 – 16.59)	-	NE	1.93 (0.85 – 4.37)	2.65 (1.01 – 6.97)	2.78 (0.28 – 27.90)
Adjusted OR (95% CI)	3.45 (1.08 – 10.99)	3.42 (0.62 – 18.85)	-	NE	0.91 (0.34 – 2.45)	2.23 (0.73 – 6.78)	2.45 (0.22 – 27.30)
Unadjusted P	0.0016	0.1576	-	-	0.1147	0.0485	0.3847
Adjusted P	0.0362	0.1584	-	-	0.8539	0.1586	0.4657
* We see that 'head to head' Vitamin C only had the lowest mortality rate, and this was statistically significant (p=0.0083)							

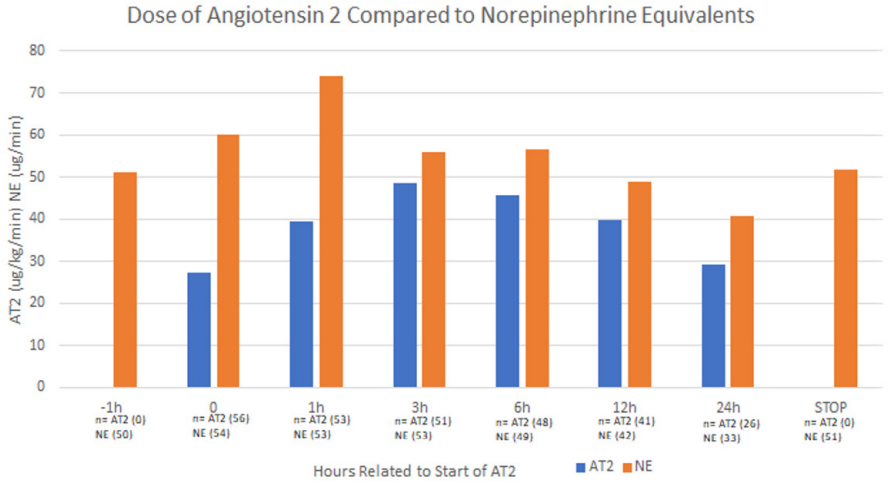

Figure 1: ATII Dose overtime.

Table 3: New Renal Replacement Therapy after initiation.

Outcome	AT II only (1)*	MB only (2)	Vit C only (3)*	AT II + Vit C (5)*	MB + Vit C (6)*	All 3 (7)	Total
Renal Replacement Therapy after Initiation	9/17 (52.9%)	0/7 (0%)	6/62 (9.7%)	12/24 (50%)	2/21 (9.5%)	0/3 (0%)	29/134 (21.6%)

*Statistical significance (P<0.01) found for varying combinations of groups: 1v3, 1v6, 3v5, 5v6.

pairwise comparisons. (Additional File 4).

Discussion

This retrospective analysis of 191 patients who required salvage therapy for refractory shock with one or a combination of the three treatments described showed that in a head to head comparison, patients treated with the combination of vitamin C, hydrocortisone, and thiamine had the lowest mortality at hospital discharge compared to treatments with AT II or MB alone (P<0.01). (Table 2) VC therapy was used significantly more as compared to the other modalities, likely stemming from its overall perception of a benign therapy and its relatively low-cost comparison. For that reason, we would assume this patient group would overall be less severely ill, however this is not supported by the average APACHE and SOFA scores calculated at ICU admission, though there is a trend towards lower scores with the VC group. (Table 1) The effect of VC protocol on mortality in severe sepsis appears significant in this retrospective review, but not fitting with findings from high quality randomized controlled trials over the past years (16, 18, 19, 20). Of note, the more recent VITAMINS randomized clinical trial, which utilized the Marik protocol, corroborated our findings and did not show any difference in vasopressor independence as well [19].

We were able to see that the overall MAP/NEE ratio increased over time with the sole use of AT2, VC, and MB respectively, which was statistically significant, but we should note that a portion of patients died in each group before the 24h mark. (Figures 1 & 2, Additional File 2) The hemodynamic response to these therapies is expected [5]. The VC only group had a significantly higher MAP at initiation and at hour 6 as compared to AT II only (p0.006 and p0.0340 respectively). This again questions the accuracy of severity of illness equivalence between the groups as well as our tendency to start VC earlier in the disease course. This review was designed to measure response within 24 hours of initiation of salvage therapy, as refractory shock and anaerobic metabolism can quickly snowball into an insurmountable acidosis and multisystem organ failure [1]. It's clear from this review that the mortality associated with refractory shock remains devastating. Although AT II has been proven to work quickly in improving hemodynamics, its effect on mortality difference was not shown here possibly owing to its late utilization and small sample size [5]. It has been suggested by some that refractory shock be treated broadly, introducing agents with different mechanisms of action together at once initially, then deescalating thereafter, similar to early goal directed therapy and broad-spectrum antibiotics approach [22,23]. The idea of sepsis and refractory shock as a complex disease process requiring multiple avenues of attack is the basis behind the seemingly random assortment of therapies in the VC protocol [16]. However, efficacy of these rescue interventions continues to be uncertain and the overall goal should be aggressive intervention at earlier stages of shock in order to prevent decompensation into refractory shock [25].

Acute renal failure is common in severe sepsis and has a significantly higher mortality associated with it as compared to acute

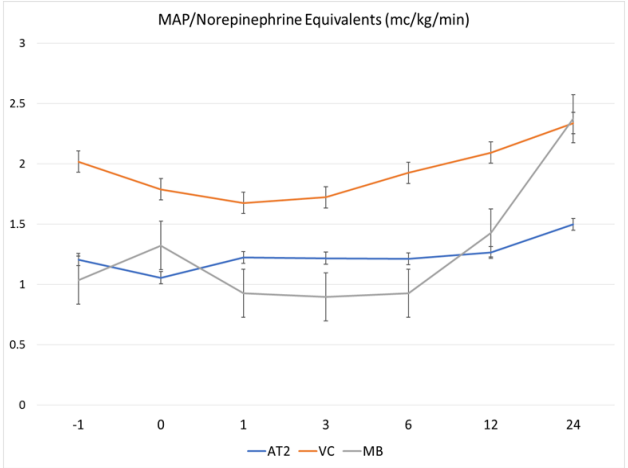

Figure 2: MAP/NEE ratio significantly increased over time for AT2, VC, and MB.

renal failure from a separate etiology [22]. This review suggested that the AT II only group had a significantly higher rate of new renal replacement therapy after initiation as compared to MB only and VC only (P=0.02, P<0.01 respectively). (Table 3) This further supports the notion that these patients were in fact sicker at baseline as compared to the VC group. Additionally, this enforces the concept that the etiology of ARF in sepsis is multifactorial, and not solely a result of renal hypoperfusion. It had been suggested by post hoc analysis of the ATHOS3 trial, that AT II potentially offered a renal protection benefit as patients on AT II came off RRT therapy faster as compared to placebo (38% vs 15%; P=0.007) (24). This review did not follow patients out to RRT liberation, but the low incidence in new onset RRT after initiation in the VC only group (9.7%) was similar to the findings from Marik et al. [16]. ICU length of stay was not significantly different across separate treatment groups, possibly owing to the large mortality rate associated with this review in conjunction with a small sample size.

The major limitation in this study is its low power. The low number of subjects overall and, particularly in the MB group, drove the statistical power down and thus increased the chance for type II error. This review had a significant amount of crossover between groups which limited our analysis. The study included all types of shock as well, which can confound results given the different treatment regimens indicated based on etiology of shock. Larger sample size could analyze the effects of these drugs more clearly. Additional limitations of this study include its nature as a retrospective review. There was not a uniform definition of refractory shock used to identify patients for the study. Patients were given interventions based on attending discretion, which can lead to selection bias. Patients were not standardized to initiation of the therapy; thus, we cannot assume that the results are equivocal across groups. Prospective trials could more clearly compare the efficacy of these salvage therapies, though because of the dynamic nature of sepsis, a uniformly efficacious agent may not be easily defined.

Strengths of our study come from its design which demonstrates firsthand how these novel therapies are utilized in a real-world clinical environment. More than just affecting MAPs, we were able to analyze how these therapies are integrated into this complex system that is severe shock while generating new questions. Further areas of inquiry include the effects of VC as a renal protective strategy in severe sepsis as well as the effect these agents have on pulmonary vasculature. This review included only a few patients with pulmonary artery catheters, but a hemodynamic modulator without pulmonary vasoconstriction would be of particular interest for future analysis. Additionally, a few patients in our study required mechanical hemodynamic support, but numbers were too low to infer any additional conclusions.

Conclusion

While several salvage therapies have shown improvement in hemodynamics in recent literature, their impact on overall mortality remains uncertain. This retrospective review demonstrated that patients treated with combination vitamin C, thiamine, and hydrocortisone had lower mortality at hospital discharge which was statistically significant when compared to patients treated with angiotensin II or methylene blue alone. These results may be affected by a baseline low survivability in this patient population and/or by not initiating these rescue therapies early enough in the disease course. More prospective studies are needed to further clarify their potential role in refractory shock.

Declarations

Ethics Approval and Consent to Participate

IRB approval through George Washington University Hospital, Study Number: 180607

Consent for Publication

DE identified data approved through IRB as above.

Availability of Data and Material

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests

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