

BRIEF REPORT

Single-Center, Real-World Observational Analysis of Angiotensin-II Salvage Therapy for Refractory Shock

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Background

Angiotensin-II was approved for use in 2017 for the treatment of vasodilatory shock. Since then, significant cost barriers have led to its use later in the pathology of shock, which is inconsistent with how the drug was initially studied.

Objectives

The purpose was to investigate the effectiveness of angiotensin-II as salvage therapy in patients with refractory shock. The primary objective was reduction in norepinephrine equivalents after angiotensin-II initiation.

Methods

This retrospective, observational analysis includes all patients who received angiotensin-II from the time of initial formulary approval (January 2019) through the time of this analysis (January 2023). The primary endpoint was absolute change in norepinephrine equivalents from initiation of angiotensin-II (hour 0) to hour three. Secondary endpoints were percent change in norepinephrine equivalents from hour 0 to 3 and patient disposition at discharge. Wilcoxon signed rank test was performed for the primary and secondary outcomes utilizing SPSS software.

Results

Twenty-one patients were included. Fourteen (67%) presented with distributive shock. At angiotensin-II initiation, 76% of patients were on at least three other vasopressors at a norepinephrine equivalent rate of 0.67 mcg/kg/min. The primary outcome was a 13% increase in norepinephrine equivalents by hour three to 0.76 mcg/kg/min. Nineteen of the 21 patients (90%) died prior to discharge, with three of those patients not surviving to hour three. A subgroup analysis of only distributive shock patients resulted in a decrease in norepinephrine equivalents of 0.06 mcg/kg/min ($p=0.374$) by hour three.

Conclusion

Angiotensin-II is ineffective when utilized later in the progression of shock.

Introduction

Angiotensin-II emerged as a groundbreaking vasoactive agent, gaining FDA approval in 2017 for the treatment of vasodilatory shock.¹ Its approval was grounded in the outcomes of the angiotensin-II for the Treatment of Vasodilatory Shock (ATHOS) and ATHOS-3 trials, providing initial insights into its efficacy.^{2,3} Subsequent studies have aimed to refine the understanding of angiotensin-II's optimal patient population and most effective timing for its initiation.⁴⁻⁸ Several analyses suggest that the greatest benefits may be yielded when administered earlier in the course of shock, especially when lower doses and numbers of vasopressors are concurrently employed.^{3,5,7,9}

Its novel mechanism of action makes it an attractive option; however, its widespread adoption has been hindered by several challenges. Chief among these is the significant acquisition cost, coupled with the absence of a clearly defined mortality benefit. Additionally, the lack of evidence comparing angiotensin-II to established standards of care for vasodilatory shock has led to hesitancy in its use across various centers. The culmination of these challenges has led healthcare providers to employ angiotensin-II as salvage therapy employed after exhausting all other viable options. This single-center observational cohort study was performed to assess the effectiveness of angiotensin-II use when implemented as salvage therapy.

Materials and Methods

This is a single-center, retrospective medical record review of all patients who received angiotensin-II infusions at a community hospital in Ocean Springs, MS from January 2019 through January 2023. All shock states were included in the analysis, and no exclusions were identified. Patient demographics, vasopressor doses, hemodynamics, admission and discharge dates, and patient death were collected. This project was approved by the Institutional Review Board.

The primary endpoint was the absolute change in norepinephrine equivalents from hour 0 to hour 3. Secondary endpoints were the percent change in norepinephrine equivalents by hour 3 and incidence of patient death. Norepinephrine equivalents were calculated as per prior publications.³ Safety outcomes were not specifically analyzed. Usual practice at this facility is to add vasopressin and hydrocortisone for distributive shock when the norepinephrine infusion reaches 30 mcg/min.

Wilcoxon signed rank test was performed for the primary and secondary outcomes using SPSS software (IBM© Version 29.0.0.0 (241)). Continuous variables with non-parametric distribution are reported as medians with interquartile ranges. Data with parametric distribution are reported as means with standard deviations. Categorical variables are reported as number and percentage. Patients who did not survive to hour three were included in

the initial calculations, but their values were removed from hour three calculations since vasopressors had been discontinued at that time. A p-value < 0.05 was considered statistically significant. Given the retrospective nature of our study, an a priori sample size was not calculated.

Results

Twenty-one patients were identified for inclusion. Their baseline characteristics are described in Table 1. The median patient age was 62 years (IQR 57-70) with an average weight of 99 kg (SD 26). A total of 16 patients (76%) had a past medical history of hypertension. Fourteen patients (67%) presented with distributive shock, followed by three each with cardiogenic and obstructive shock (14%) and one hemorrhagic shock (5%). All patients were initiated on 20 ng/kg/min and titrated to a median dose of 80 ng/kg/min (IQR 50-80) with a median angiotensin-II duration of 16 hours (IQR 4-24). At the time of angiotensin-II initiation, 76% of patients (N = 16) were on at least 3 other vasopressors at a norepinephrine equivalent rate of 0.67 mcg/kg/min.

The primary outcome revealed an increase in norepinephrine equivalents from 0.67-0.76 mcg/kg/min by hour 3 (p = 0.326). The secondary outcome of percent reduction in norepinephrine equivalents by hour three revealed an increase of 12%. Nineteen of the 21 patients died (90%), with three patients not surviving to hour three.

A subgroup analysis of only distributive shock patients was completed (n = 14). (Table 2) This patient subgroup was on an average of 2.7 vasopressors (SD 0.73) prior to angiotensin-II initiation with 71% of patients on at least three. The absolute and percent reduction in norepinephrine equivalents at three hours was 0.06 mcg/kg/min (p = 0.374), and 11%, respectively.

Discussion

Since the approval of angiotensin-II, multiple studies have been conducted to ascertain the optimal patient population for the medication's utilization. These investigations have revealed varying effects associated with different dosages of the drug. Prior studies indicating benefits with angiotensin-II often involved patients on baseline doses of norepinephrine equivalents <0.6 mcg/kg/min, whereas the median norepinephrine equivalents at baseline in this study were 0.67 mcg/kg/min.^{3,5,6,8} Analyses by Wieruszewski and Smith highlighted benefits at even lower doses of <0.25 mcg/kg/min and <0.2 mcg/kg/min, respectively.^{5,9} None of the patients in the current analysis were on doses below 0.2 mcg/kg/min.

Moreover, the number of vasopressors administered prior to angiotensin-II initiation appears to be a crucial factor. In this study, 76% of patients were on three or more vasopressors before angiotensin-II was initiated, a notable contrast to the ATHOS-3 trial where only 20% of patients fell into this

Table 1. Baseline Characteristics of Patients Receiving Angiotensin-II

Characteristic	(N = 21)
Age, years, median (IQR)	62 (72-70)
Male, no. (%)	11 (52)
Weight, kg, mean (SD)	99 (26)
Past Medical History, No. (%)	
Hypertension	16 (76)
Diabetes Mellitus	6 (29)
Coronary Artery Disease	6 (29)
Etiology of Shock, No. (%)	
Distributive (septic)	14 (67)
Cardiogenic	3 (14)
Obstructive	3 (14)
Hemorrhagic	1 (5)
Number of Vasopressors Prior to Angiotensin-II, Mean (SD)	3 (0.97)
Distribution, No. (%)	
0	0 (0)
1	2 (10)
2	3 (14)
3	11 (52)
≥ 4	5 (24)
Baseline Norepinephrine Equivalent Dose	
Median (IQR)	0.67 (0.38-1.1)
Distribution, No. (%)	
< 0.2	0 (0)
≥ 0.2 to < 0.5	7 (33)
≥ 0.5	14 (67)
Angiotensin II Characteristics, median (IQR)	
Initial Angiotensin-II Dose, ng/kg/min	20 (NA)
Maximum Angiotensin-II Dose, ng/kg/min	80 (50-80)
Duration of Angiotensin-II Therapy, hours	17 (3.5-23.8)

category.³ Smith et al demonstrated a more comparable population, with 69% of patients on three or more vasopressors at initiation.⁵ However, baseline norepinephrine equivalent doses in their study were lower at 0.55 mcg/kg/min, and it was noted that the most remarkable effect was seen in patients receiving <0.2 mcg/kg/min.⁵ Although insignificant, the current analysis actually showed an increase in norepinephrine equivalents by hour three, even with escalating angiotensin-II doses. There was no significant decrease in norepinephrine equivalents, implying a lack of meaningful hemodynamic benefits.

While other studies have utilized mean arterial pressure (MAP) as an additional measure of effect, this analysis did not.^{2,3,5,6,8,9} This was based on the authors' discretion, since when titrated appropriately per MAP goals, vasopressor doses should be a reliable indicator of efficacy.

Table 2. Demographics of Patients with Distributive Shock

Variables	(N = 14)
Number of Vasopressors Prior to Angiotensin-II, Mean (SD)	2.7 (0.73)
Distribution, No. (%)	
0	0 (0)
1	1 (7)
2	3 (21)
3	9 (64)
≥ 4	1 (7)
Baseline Norepinephrine Equivalent Dose, mcg/kg/min, Median (IQR)	0.56 (0.34-1.1)
Distribution No. (%)	
< 0.2 mcg/kg/min	0 (0)
≥ 0.2 to < 0.5 mcg/kg/min	6 (43)
≥ 0.5 mcg/kg/min	8 (57)
Disposition, No. (%)	
Survived	1 (7)
Deceased	13 (93)

Two studies highlighting potential mortality benefits associated with angiotensin-II revealed specific patient subgroups that demonstrated favorable outcomes.^{4,10} Specifically, patients undergoing renal replacement therapy and those with elevated renin levels had the most promising results.^{4,10} Another analysis by Wieruszewski et al. discovered that patients with lower lactate levels and those concurrently receiving vasopressin were more likely to exhibit a positive response at three hours and survival at 30 days.⁶ Of the two surviving patients in this study, one presented with cardiogenic shock, while the other presented with distributive shock secondary to pyelonephritis. In the latter instance, angiotensin-II was initiated as the 2nd vasopressor when norepinephrine was at 0.25 mcg/kg/min. This example supports the observation that angiotensin-II is more effective in early shock as opposed to vasopressor-refractory shock.

Limitations

Potential limitations of this study include the lack of analysis of home medications for potential angiotensin receptor blockers at baseline and lack of documentation of the use of rescue medications, like corticosteroids, commonly used in refractory septic shock. Incidence of renal replacement therapy and lactate and renin levels were also not collected. Since most patients in this analysis did not improve hemodynamically, and ultimately died, we did not collect specific safety events. The retrospective design of this study presents an additional limitation due to the potential for missing data points and documentation. Lastly, the small sample size may have prevented the observation of significant outcomes that may have been seen in larger samples.

Conclusion

The addition of angiotensin-II in this patient population did not result in meaningful improvements in hemodynamics or patient outcomes. Based on the results of this study in combination with prior analyses, it is our conclusion that angiotensin-II is ineffective when used in refractory shock states. These findings and results of prior trials underscore the importance of considering patient-specific factors when assessing the impact of angiotensin-II on distributive shock. More exploration should be performed to determine the best patient population in which to utilize angiotensin-II.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Singing River Health System (no. 00004249) on November 8, 2022, with the need for written informed consent waived.

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