Journal of Shock and Hemodynamics

Volume 2 | Issue 1 Article 3

2023

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Recommended Citation

Ellena, Kamah J.; Combs, Jenna L.; Draper, Heather M.; and Belfer, Julie J. (2023) "Role of Midodrine on Vasopressor Duration in Patients with Sepsis," *Journal of Shock and Hemodynamics*: Vol. 2(1) :E2023213
DOI: https://doi.org/10.58464/2836-0605.1041

Available at: https://digitalcommons.library.tmc.edu/josh/vol2/iss1/3

Original Research

Role of Midodrine on Vasopressor Duration in Patients with Sepsis

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Received June 6, 2023
Accepted November 6, 2023
Published December 1, 2023

Abstract

Existing literature evaluating the off-label use of midodrine has focused primarily on postoperative hypotensive patients requiring a single vasopressor. This study aimed to evaluate the impact of midodrine on vasopressor duration and length of stay in patients receiving vasopressors for sepsis-related hypotension. This is an institutional review board-approved, single-center, retrospective analysis of critically ill patients with hypotension secondary to sepsis who received midodrine and intravenous vasopressors compared to those who received intravenous vasopressors alone. Patients were matched by Acute Physiology and Chronic Health Evaluation II score, suspected source of infection, and presence of bacteremia. One hundred patients were included in this analysis. The median duration of vasopressors in the midodrine group (n = 50) was 36 hours (interquartile range [IQR] 18.94-61.94) compared to 26 hours (IQR 13.75-59.88) in the vasopressor-only group (P = .127). Patients in the midodrine group were in the intensive care unit (ICU) for a median of 3.9 days compared to 2.6 days in the vasopressor-only group (P = .017). Midodrine patients had a median hospital length of stay 3.7 days longer than the vasopressor-only group (P = .008). Eight patients (16%) were discharged on midodrine without an indication for therapy. This report assesses the use of midodrine in patients with sepsis requiring one or more vasopressors. Initiation of midodrine did not decrease the time to vasopressor discontinuation. The evaluation of midodrine indication and potential for its discontinuation is an intervention pharmacists can target at the transition of care from the ICU.

Keywords: critical care, intensive care unit, midodrine, vasopressors, sepsis, transitions of care myocardial protection, ischemia-reperfusion injury

Introduction

Intravenous (IV) vasopressors are integral in the management of patients with sepsis experiencing persistent hypotension following adequate volume resuscitation.[1] Although associated with a survival benefit, vasopressors may cause serious adverse effects and have many administration considerations. Admission to the intensive care unit (ICU) is often required for frequent hemodynamic and peripheral or visceral ischemia monitoring during the administration of IV vasopressor therapy.[2] To optimize safety, administration through a central venous catheter is recommended; however, long-term use of these access devices may increase the risk of central line-associated bloodstream infection, which carries a 12-25% mortality rate.[2,3] Vasopressor administration can become a barrier to disposition in patients who have otherwise improved but continue to require ongoing low doses of vasopressor support.

In recent years, midodrine has gained popularity as an adjunct in weaning IV vasopressors to limit the risk of serious

adverse effects associated with vasopressor use and reduce ICU length of stay (LOS). Midodrine is an oral alpha-1 agonist with a labeled indication for the treatment of orthostatic hypotension. It is a prodrug that undergoes enzymatic hydrolysis to form its active metabolite, desglymidodrine.[4,5] As an agonist on both arterial and venous alpha-adrenergic receptors, desglymidodrine works peripherally to increase blood pressure, increasing vascular tone without direct cardiac effects.[5] The side effect profile of midodrine is considered safer than that of vasopressors, with the most common adverse effects being sympathomimetic, including supine hypertension, paresthesia, and vagal reflex bradyarrhythmias.[5]

In patients requiring hemodynamic support to facilitate the weaning of vasopressors, midodrine administration can minimize the adverse effects of IV vasopressors, decrease ICU LOS, and provide cost savings. Clinical trial data supporting the use of midodrine to wean vasopressors in medical ICU patients diagnosed with sepsis is limited. Most research has limited study populations regarding perioperative hypotension management; many protocols included patients requiring a single vasopressor and excluded those requiring high-dose vasopressors.[6,7] Additionally, few studies use matched-patient populations to account for varying levels of critical illness. The purpose of this study is to assess how the initiation of midodrine affects vasopressor weaning in patients who are receiving IV vasopressor therapy for hypotension secondary to sepsis.

Methods

Study Design and Setting

This retrospective cohort study included adult patients admitted to the mixed medical/surgical ICU between February 1, 2019, and November 30, 2020, at a 350-bed community teaching hospital. This study was approved by the institution's Institutional Review Board (IRB) with a waiver of informed consent. All work was conducted in compliance with the IRB requirements.

Study Participants

Patients aged 18 years or older were eligible for inclusion if they were admitted to the ICU, had a diagnosis of sepsis, and received one or more IV vasopressors (i.e., dopamine, epinephrine, norepinephrine, phenylephrine, vasopressin) for at least eight hours. Patients were excluded if they expired within 24 hours of ICU admission, transferred from another facility, received concomitant IV inotrope support, or received midodrine before admission. A patient list was generated through a query of the electronic medical record (EMR) based on the International Classification of Diseases, 10th Revision codes involving sepsis on admission.

Patients meeting eligibility criteria were separated into two groups: midodrine or vasopressor monotherapy. Patients in the midodrine group had to receive at least three doses to be included. The primary investigator collected all data retrospectively utilizing the institution's EMR. To ensure that acuity of illness was consistent between groups, patients were matched for inclusion based on Acute Physiology and Chronic Health Evaluation (APACHE) II score within the first 24 hours of admission, suspected source of infection, and presence of bacteremia.

Statistical Analysis

A sample size of 100 patients was calculated to detect a 10% absolute difference in vasopressor duration using a two-sided test with $\alpha = 0.05$ and $\beta = 0.2$. Fifty patients were included in both groups (Figure 1). Baseline demographic data were reported with descriptive statistics. Nominal data were compared using the X^2 or Fisher's exact test, and interval data were compared using Student's t-test and Mann-Whitney U test, as appropriate. A P value of $< .05$ was considered statistically significant. All statistical analyses were performed using SPSS software, version 22 (IBM, Corporation, Armonk, NY).

Outcomes

The primary objective of this study was to compare the time (in hours) to vasopressor discontinuation in patients with hypotension secondary to sepsis undergoing vasopressor weaning with or without the use of midodrine. Vasopressor discontinuation was defined as a vasopressor-free interval of at least 8 hours. Secondary objectives included the comparison of cumulative IV vasopressor doses, ICU and hospital LOS, and the cost of therapy between groups. Vasopressor dose conversions were performed using norepinephrine equivalents consistent with previous literature assessing midodrine in vasopressor weaning (Table 1).[8] The cost of therapy was calculated by attaining the total number of doses of IV vasopressor and midodrine administered and multiplying by the medication acquisition cost (average wholesale price). This calculation was conservative and did not include the cost of compounding materials, administration supplies, or nursing time. Patients within the midodrine group were assessed via discharge documentation and prescription fill history review to determine the continuation of midodrine after hospital discharge. Additionally, patients who received midodrine at hospital discharge were followed for up to one year to characterize the use of midodrine following ICU and hospital discharge.

Table 1. Vasopressor dose conversions based on norepinephrine equivalents

Agent	Norepinephrine Equivalent
Norepinephrine	0.1 mcg/kg/min
Dopamine	15 mcg/kg/min
Epinephrine	0.1 mcg/kg/min
Phenylephrine	1 mcg/kg/min
Vasopressin	0.04 units/min

Results

Patient Characteristics

A total of 632 patients were screened for study eligibility until the sample size of 100 patients was met. The most common reasons for exclusion are listed in Figure 1. Baseline characteristics were similar between the two groups (Table 2). The mean APACHE II score for each group was 22 (± 9.21), and the most common sources of infection were respiratory and genitourinary.

Outcomes

In the midodrine group, the duration of vasopressor therapy was a median of 36 hours (interquartile range [IQR] 18.94-61.94) compared to 26 hours (IQR 13.75-59.88) in the vasopressor-only group (P = .127). The most utilized vasopressor regimen was norepinephrine monotherapy, followed by norepinephrine in combination with vasopressin (Table 3). In the midodrine group, 70% received norepinephrine monotherapy. Alternate IV vasopressor regimens consisted of two or more agents and often contained vasopressin. Individual doses of midodrine ranged from 2.5 mg to 30 mg, and dosing intervals ranged from every 6 hours to every 12 hours. The most common midodrine dosing regimen was 10 mg every 8 hours.

When assessing LOS, patients in the midodrine group were in the ICU for a median of 3.9 days compared to 2.6 days in the vasopressor-only group (P = .017). Midodrine patients also had a median hospital LOS that was 3.7 days longer than the vasopressor-only group (P = .008). The median cost of therapy for the midodrine group was lower ($18.13) than the vasopressor-only group ($36.73), but it was not statistically different (P = .495).

Eight (16%) patients in the midodrine group were discharged from the hospital with a prescription for midodrine therapy. Of these eight patients, three continued to receive midodrine prescriptions from their primary care provider one year after discharge. Of the remaining patients, two filled midodrine until patient expiration thirty days after discharge, two were lost to follow-up, and one had midodrine discontinued by their primary care physician.

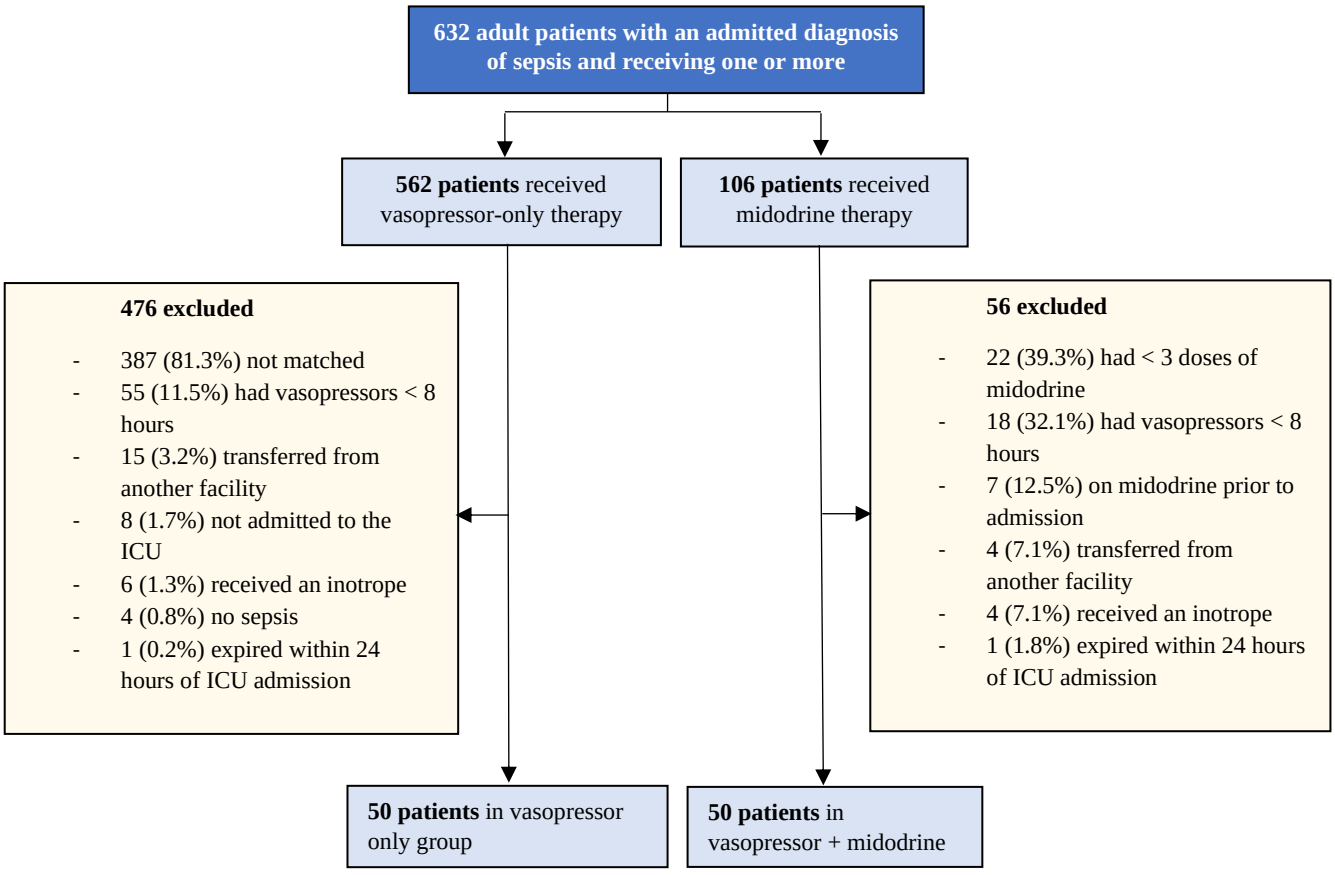

Figure 1. Enrollment and group selection.

Table 2. Baseline patient characteristics of the study cohort.

Variable	Midodrine (n = 50)	Vasopressor Only (n = 50)	P value
Age, years, mean (±SD)	63 (±14)	61 (±14)	.945
Male, n (%)	33 (66)	32 (64)	.834
Weight, kg, mean (±SD)	86 (±23)	87 (±27)	.400
Hydrocortisone, n (%)	15 (30)	15 (3)	1.000
Expired during hospital admission, n (%)	17 (34)	18 (36)	.834
COVID positive, n (%)	3 (6)	5 (10)	.715
APACHE II, mean (±SD)	22 (±9)	22 (±9)	1.000
Bacteremia present, n (%)	11 (±22)	11 (±22)	1.000
Number of midodrine doses administered, median (IQR)	9 (6-18)	N/A	N/A
Midodrine administered, total mg, median (IQR)	93 (50-236)	N/A	N/A
Source of Infection, n (%)			
Respiratory	19 (38)	19 (38)	1.000
Genitourinary	12 (24)	12 (24)	1.000
Intra-abdominal	8 (16)	8 (16)	1.000
Skin and soft tissue	3 (6)	3 (6)	1.000
Central line-associated bacteremia	1 (2)	1 (2)	1.000
Unknown	7 (14)	7 (14)	1.000

Table 3. Vasopressor regimens utilized in the study population.

Vasopressor Selection	Midodrine (n = 50)	Vasopressor Only (n = 50)	P value
Norepinephrine, n (%)	35 (70)	24 (48)	
Norepinephrine + vasopressin, n (%)	7 (14)	11 (22)	
Three vasopressors, n (%)	5 (10)	6 (12)	
Other, n (%)	3 (6)	9 (18)	
Norepinephrine equivalents, mcg, median (IQR)	10232 (4796 - 32755)	15487 (4405 - 40993)	.521
Vasopressor, hours, median (IQR)	36 (19 - 62)	26 (14 - 60)	.127

Discussion

This study is unique compared to prior research in that it targets the use of midodrine in the sepsis population while previous literature focuses on midrodrine's use in the setting of perioperative hypotension or in patients with shock from multiple etiologies. Our study demonstrated no benefit from the use of midodrine in vasopressor duration for patients with hypotension attributed to sepsis.

Santer et al. found no difference in the time to vasopressor discontinuation when comparing midodrine to placebo as an adjunct to standard treatment in a predominantly postoperative or surgical ICU population receiving one vasopressor.[6] A retrospective cohort study found a significant decrease in the number of patients on vasopressors 24 hours after starting midodrine in a mainly surgical ICU setting.[8] Few studies have assessed midodrine in patients requiring more than one vasopressor, and many have commonly excluded those requiring multiple or high-dose vasopressors.[6,7,9,10] El Adly et al. evaluated the use of midodrine in septic shock but included only patients requiring a single vasopressor agent.[11]

Our study included patients requiring multiple vasopressors and high-dose vasopressors to address the current gap in literature. This is reflected in our study's patient population, which had a higher acuity than that of previous studies. Our research included patients with higher APACHE II scores (mean = 22, signifying a 40% nonoperative risk of mortality) and did not exclude patients experiencing septic

shock, in contrast to prior studies.[6-8,10,12] In the MIDAS trial, the patient population had an average APACHE II score of 14 (15% nonoperative risk of mortality), and Levine et al.'s study consisted of patients with an average score of 18 (24% nonoperative risk of mortality).[6,7] Levine et al. and an observational study by Poveromo et al. both had unequal administration of corticosteroids between the midodrine and vasopressor groups.[7,13] Of note, in this analysis, there was equal administration of stress dose steroids in each group, eliminating a confounder identified in prior midodrine studies.

Although there was no statistically significant difference in cost, more patients in the vasopressor-only group received vasopressin therapy in combination with another agent. The cost analysis was conducted to assess the impact of the price increase of vasopressin as well as the potential cost savings of midodrine, particularly if a vasopressor-sparing effect was found. All therapeutic agents assessed are available as generic formulations and are relatively inexpensive, except for vasopressin. From 2010 to 2016, the price of vasopressin increased by 1138%, rising from $12.83 to $158.83 per vial.[14] The cost analysis conducted in this study was based solely on vasopressor and midodrine drug acquisition costs. The costs of medication preparation, administration, nursing care, and ICU hospitalization were not included in the total therapy cost. Due to the longer ICU and hospital LOS in the midodrine group, there may be a larger total treatment cost difference between the groups that was not captured in our analysis.

This analysis found that midodrine was continued at discharge in 16% of patients. Continuing medications that are no longer indicated is common among other medical management practices at transitions of care. Medications initiated in the ICU for stress ulcer prophylaxis and delirium are often continued when transferred out of the ICU or at hospital discharge. Kumar et al. assessed 1529 ICU patients started on stress ulcer prophylaxis and found that 23.6% of the patients were inappropriately discharged on a proton pump inhibitor.[15] Fiorenza et al. came up with a similar result when investigating the use of quetiapine and haloperidol, discovering that 56% of patients discharged from hospital on quetiapine were without an indication.[16] Prolonged midodrine administration without a compelling indication increases the risk of developing adverse effects, such as a hypertensive emergency. One study observed that midodrine continuation at the time of hospital discharge was associated with increased mortality at one year.[17] These findings highlight the need for assessing medication appropriateness at each transition of care.

Consideration should be given to the limitations of this study. It is retrospective in nature, relying on appropriate documentation within the medical record. This analysis was not blinded by the treatment group during screening for inclusion, which could lead to selection bias. To limit this bias, the patients were selected from a randomized list until the required sample size was met. To eliminate confounders, the patients were matched between groups to ensure similar severity of illness and infection presentation, allowing for a more accurate assessment of the role of midodrine in vasopressor weaning.

Midodrine dosing and titration were left to clinician discretion and were neither protocolized nor randomized. The most common midodrine dosing strategy was 10 mg every 8 hours. This may not be an optimal dosing strategy due to the pharmacokinetic profile of midodrine.[18] A recent review article suggested initiating the therapy at almost double our average dose, with a starting midodrine dose of 20 mg every 8 hours, up-titrating in 5 to 10 mg increments to a maximum of 40 mg every 8 hours.[19]

A further limitation of this analysis was that the vasopressor administration prior to the initiation time of midodrine was not a collected data point. Previous midodrine studies have found two midodrine initiation strategies: early administration in sepsis to limit the number of vasopressors used and later administration during hypotension recovery to assist with liberation in patients with low-dose vasopressor requirements.[9]

Lastly, this study did not include compounding materials, administration supplies, and nursing time costs. Recognizing these associated costs increase the cost of medication administration, this cost would apply to both groups and would not likely have meaningful implications.

Conclusion

The initiation of midodrine in patients undergoing IV vasopressor wean was not associated with a reduction in time to IV vasopressor discontinuation or medication cost of therapy in patients with sepsis. Patients receiving midodrine therapy experienced both a longer ICU and hospital LOS. Care teams should play a role in evaluating patients' conditions started on midodrine during transitions of care to assist with appropriate discontinuation of the therapy. Future studies should consider a prospective design focusing on the timing of midodrine initiation, optimal dosing, and vasopressor utilization.

Disclosures

None

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