2018

# Addition of midodrine in ICU patients and the impact on vasopressor tapering

Leslie Siegel PharmD

# Addition of Midodrine in ICU Patients and the Impact on Vasopressor Tapering

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The speaker has no actual or potential conflict of interest in relation to this presentation.

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# Objectives

- Evaluate current literature surrounding midodrine use within an ICU setting
- Discuss the goals and objectives of this project
- Review methodology
- Share study results
- Discuss how findings may shape current practice

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# Background

- ¼ of ICU patients require vasopressors

- Midodrine is an alpha-1 agonist
  - FDA indication: orthostatic hypotension
  - Off-label: syncope

Thongprayoon C, et. Al. Temporal trends in the utilization of vasopressors in intensive care units: an epidemiologic study. *BMC Pharmacology Toxicology.* 2016; 17 (19).

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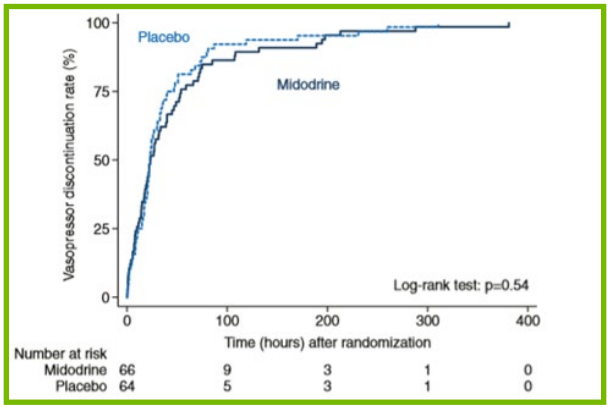
# Literature: MIDAS Trial

- Design:
  - Randomized Control
  - Inclusion: >/= 18 years of age, single vasopressor therapy > 24 hours
  - Exclusion: evidence of inadequate tissue oxygenation, adrenal insufficiency, liver failure, sCr > 2 mg/dL, and severe organic heart disease
- Results:
  - 136 patients included
  - Primary outcome: time to vasopressor discontinuation
  - Secondary outcome: ICU length of stay (LOS), hospital LOS, ICU readmissions
  - No significant difference




Santer P, et. al. Effect of Midodrine versus placebo on time to vasopressor discontinuation in patients with persistent hypotension in the intensive care units (MIDAS): an international randomized clinical trial. *Intensive Care Medicine.* 2020

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# Literature: Midodrine and Sepsis

- Design:
  - Retrospective chart analysis
  - Inclusion: sepsis, IV vasopressors >/= 24 hours, initial midodrine dose >/= 10 mg every 8 hours
- Results:
  - 275 included (135 received midodrine)
  - Midodrine associated with 24% reduction in vasopressor duration
  - Midodrine associated with 20% reduction in ICU LOS

| Variables | IV Vasopressor Only (n= 140) | IV Vasopressor With Midodrine (n= 135) | *P* Value |
|---|---|---|---|
| IV vasopressor duration, d | 3.8 | 2.9 | < .001 |
| IV vasopressor reinstitution, No. (%) | 21 (15) | 7 (5.2) | .007 |
| Change in creatinine, mg/dL, SD | 0.8 ± 1.6 | 0.5 ± 1.3 | .048 |
| ICU LOS in days, (mean, SD) | 9.4 ± 6.7 | 7.5 ± 5.9 | .017 |
| Hospital LOS in days (mean, SD) | 24.2 ± 14.3 | 21.9 ± 14.4 | .3 |
| ICU mortality | 26 (18.6%) | 15 (11.1%) | .08 |
| Hospital mortality | 36 (25.7%) | 31 (23%) | .6 |

LOS = length of stay.

Whitson MR, et. al. Feasibility, Utility, and Safety of Midodrine During Recovery Phase from Septic Shock. *Chest.* 2016; 149 (6): 1380-3

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# Self-Assessment Question #1

Midodrine's Mechanism of action is closely related to which vasopressor?

a) Phenylephrine
b) Norepinephrine
c) Dobutamine
d) Vasopressin

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# Self-Assessment Question #2

What is an approved FDA indication for midodrine?

a) Syncope

b) Orthostatic hypotension

c) Hypotension related to dialysis

d) Vasopressor tapering

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# Study Purpose and Design

This project was deemed exempt from review by the Institution Review Board (IRB) by the institution's IRB screening process.

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# Goals

- Benefits:
  - Build on current literature to determine the impact of midodrine in vasopressor tapering
  - Quantify midodrine benefit by assessing phenylephrine equivalents
  - Identify populations who may benefit from midodrine

- Risks
  - Assess for safety concerns with vasopressor tapering with midodrine

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# Setting

## Parkview Health

- Not-for-profit, community-owned organization
- Northeast Indiana and northwest Ohio
- 10 hospital health system
  - 3 hospitals have an ICU
    - Parkview Regional Medical Center
    - Parkview Randallia
    - Parkview Dekalb


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# Design

- Retrospective match cohort analysis
- Location: Parkview's system-wide ICU capable hospitals
  - PRMC
  - PVH
  - PDH
- 2-year timeframe
  - 8/1/2018 – 8/1/2020

**Group 1**

- Vasopressor

**Group 2**

- Vasopressor + midodrine

**Sub-analysis groups**

- Patients with midodrine prior to admission
- Dialysis patients
- Vasopressor indication
- Cirrhosis patients

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# Patient Eligibility

## Inclusion Criteria

- Parkview systemwide
- >/= 18 years of age
- >/= 12 hours of continuous vasopressor support*
- Initiated on midodrine with concurrent vasopressor therapy

## Exclusion Criteria

- Intermittent vasopressor/midodrine therapy
- Received fewer than 3 doses of midodrine
- Pregnancy
- Syncope

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* Included vasopressors: dopamine, epinephrine, norepinephrine, phenylephrine, and vasopressin

# Endpoints

- **Primary: Quantify the change in vasopressor requirements at 12 and 24 hours after midodrine initiation**

- Secondary*:
  - Duration of vasopressor therapy
  - ICU and hospital length of stay
  - Frequency of vasopressor re-initiation
  - ICU readmission rates
  - ICU/hospital mortality
  - 30-day mortality

* All secondary outcomes compare patients with concomitant midodrine and vasopressors to patients receiving vasopressors alone

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# Phenylephrine Equivalents

| Vasopressor | Dose equivalent to 1 mcg/min Phenylephrine |
|---|---|
| Dopamine | 10 mcg/min |
| Norepinephrine | 0.1 mcg/min |
| Epinephrine | 0.1 mcg/min |
| Vasopressin | 0.0002 units/min |
| Phenylephrine | 1 mcg/min |

Poveromo LB, et. al. Midodrine for the Weaning of vasopressor therapy. *Journal of Clinical Pharmacy and Therapeutics.* 2016; 41: 260-265.

# Study Results

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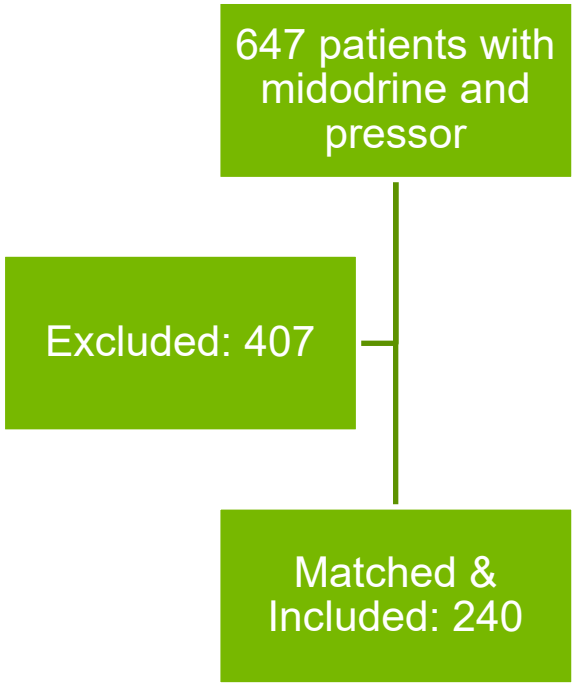
# Screening




**Total enrolled: 480**

**Reason for exclusion:**

- 112: Vasopressor <12 hours
- 92: Midodrine and vasopressor were not concurrent
- 83: Midodrine prescribed as needed
- 68: <3 doses of midodrine
- 45: Unable to Match
- 7: Syncope

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# Demographics

| | EXPERIMENTAL (n=240) | CONTROL (n=240) |
|---|---|---|
| Age (years) | 65.4 ± 13.6 | 65.4 ± 13.6 |
| Male | 120 (50.0%) | 120 (50.0%) |
| Caucasian | 207 (86.3%) | 214 (89.2%) |
| Dialysis | 51 (21.3%) | 51 (21.3%) |
| Cirrhosis | 34 (14.2%) | 34 (14.2%) |
| Midodrine PTA | 26 (10.8%) | N/A |
| Concurrent Steroids | 113 (47.1%) | 93 (38.8%) |
| **Shock Type** | | |
| • *Distributive* | 171 (71.3%) | 171 (71.3%) |
| • *Hypovolemic* | 35 (14.6%) | 35 (14.6%) |
| • *Cardiogenic* | 25 (10.4%) | 25 (10.4%) |
| • *Neurogenic* | 9 (3.8%) | 9 (3.8%) |

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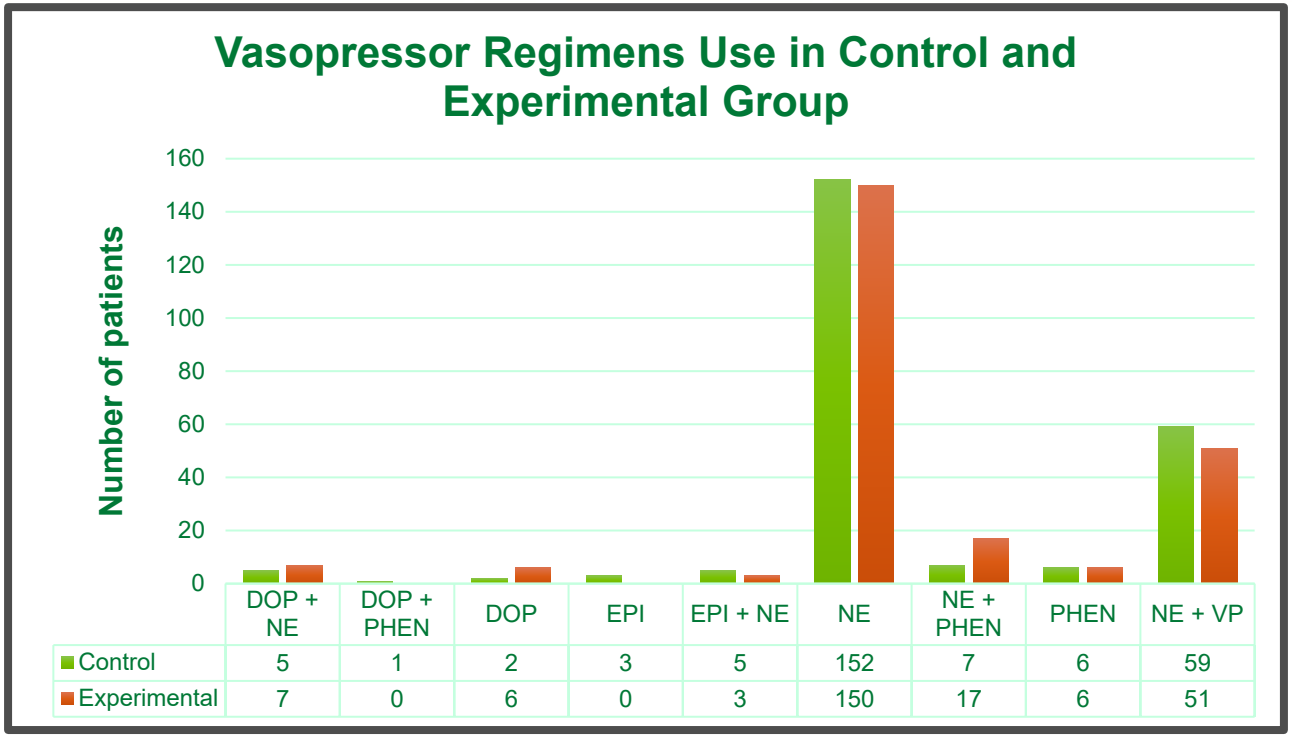
# Vasopressor Regimens




Included vasopressors: dopamine (DOP), epinephrine (EPI), norepinephrine (NE), phenylephrine (PHEN), and vasopressin (VP)

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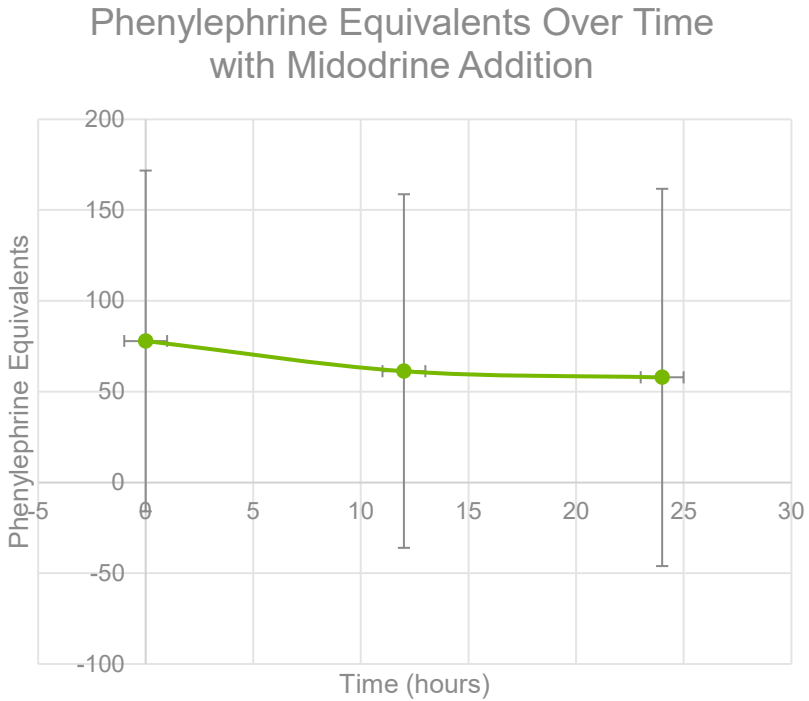
# Results – Primary Outcome




**Midodrine was associated with a significant reduction in vasopressors at 12 and 24 hours.**

| Time | Phenylephrine Equivalents | P value |
|---|---|---|
| Baseline | 77.9 ± 93.9 | |
| 12 hours | 61.3 ± 97.4 | 0.0002 |
| 24 hours | 57.9 ± 103.9 | 0.0004 |

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# Results – Secondary

| | N=240 Midodrine | N=240 Control | P value |
|---|---|---|---|
| Total Pressor Duration (days) | 6.0 ± 6.3 | 3.2 ± 3.9 | <0.001 |
| Pressor Reinitiating | 1.7 ± 2.4 | 0.8 ± 1.2 | <0.001 |
| ICU/progressive care LOS (days) | 10.4 ± 9.14 | 6.0 ± 6.3 | <0.001 |
| Hospital LOS | 14.0 ± 10.6 | 11.3 ± 9.1 | 0.0035 |
| Hospital mortality | 30 (12.5%) | 30 (12.5%) | 1 |
| 30-day mortality | 87 (36.3%) | 33 (13.8%) | <0.001 |
| SBP >160 mmHg during admission | 126 (52.5%) | 15 (0.9%) | <0.001 |

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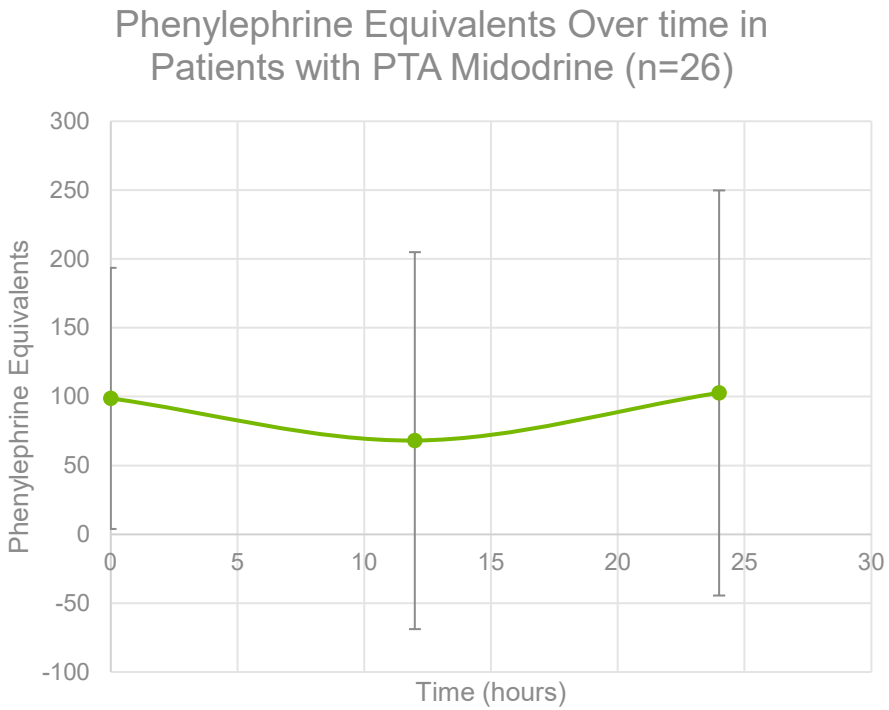
# Sub-analysis: Midodrine PTA (n=26)




**Midodrine did not have a significant reduction in phenylephrine equivalents at 12 or 24 hours**

| Time | Phenylephrine Equivalents | P value |
|---|---|---|
| Baseline | 100.6 ± 93.3 | |
| 12 hours | 68.1 ± 136.8 | 0.146 |
| 24 hours | 102.7 ± 147.1 | 0.926 |

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# Sub-analysis: Midodrine PTA

| | N=26 Midodrine | N=26 Control | P value |
|---|---|---|---|
| Age | 61.3 ± 15.1 | 61.0 ± 14.8 | |
| Max Daily Midodrine Dose (mg) | 33.8 ± 13.9 | NA | |
| Cirrhosis | 8 (30.7%) | 8 (30.7%) | |
| Dialysis | 11 (32.4%) | 11 (32.4%) | |
| Concurrent Steroids | 11 (32.4%) | 10 (38.4%) | |
| Total Pressure Duration (days) | 5.1 ± 5.8 | 3.7 ± 4.3 | 0.301 |
| Pressor Reinitiating | 1.0 ± 1.6 | 1.0 ± 1.0 | 0.918 |
| ICU/progressive care LOS (days) | 8.3 ± 7.9 | 8.4 ± 9.6 | 0.967 |
| Hospital LOS | 12.3 ± 9.9 | 12.8 ± 9.6 | 0.870 |
| Hospital mortality | 7 (26.9%) | 7 (26.9%) | 1 |
| 30-day mortality | 14 (53.8%) | 8 (30.8%) | 0.092 |

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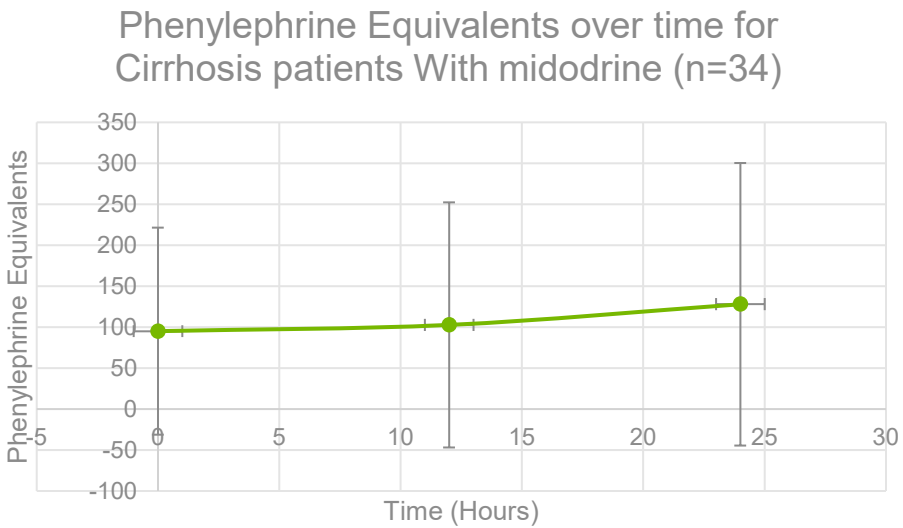
# Sub-analysis: Cirrhosis (n=34)




**Midodrine did not have a significant reduction in phenylephrine equivalents at 12 or 24 hours**

| Time | Phenylephrine Equivalents | P value |
|---|---|---|
| Baseline | 95 ± 126.4 | |
| 12 hours | 102.7 ± 149.5 | 0.659 |
| 24 hours | 127.9 ± 172.3 | 0.205 |

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# Sub-analysis: Cirrhosis

| | N=34 Midodrine | N=34 Control | P value |
|---|---|---|---|
| Age | 57.5 ± 16.2 | 56.5 ± 15.7 | |
| Max Daily Midodrine Dose (mg) | 31.5 ± 14.6 mg | N/A | |
| Dialysis | 9 (26.5%) | 9 (26.5%) | |
| Concurrent Steroids | 11 (32.4%) | 14 (41.2%) | |
| Total Pressor Duration (days) | 4.5 ± 4.9 | 3.4 ± 4.4 | 0.352 |
| Pressor Reinitiating | 1.0 ± 1.6 | 0.9 ± 1.02 | 0.9185 |
| ICU/progressive care LOS (days) | 8.0 ± 6.6 | 7.9 ± 7.3 | 0.662 |
| Hospital LOS | 12.5 ± 10.2 | 10.6 ± 8.3 | 0.392 |
| Hospital mortality | 7 (20.6%) | 13 (38.2%) | 0.110 |
| 30-day mortality | 16 (47.1%) | 17 (50%) | 0.808 |

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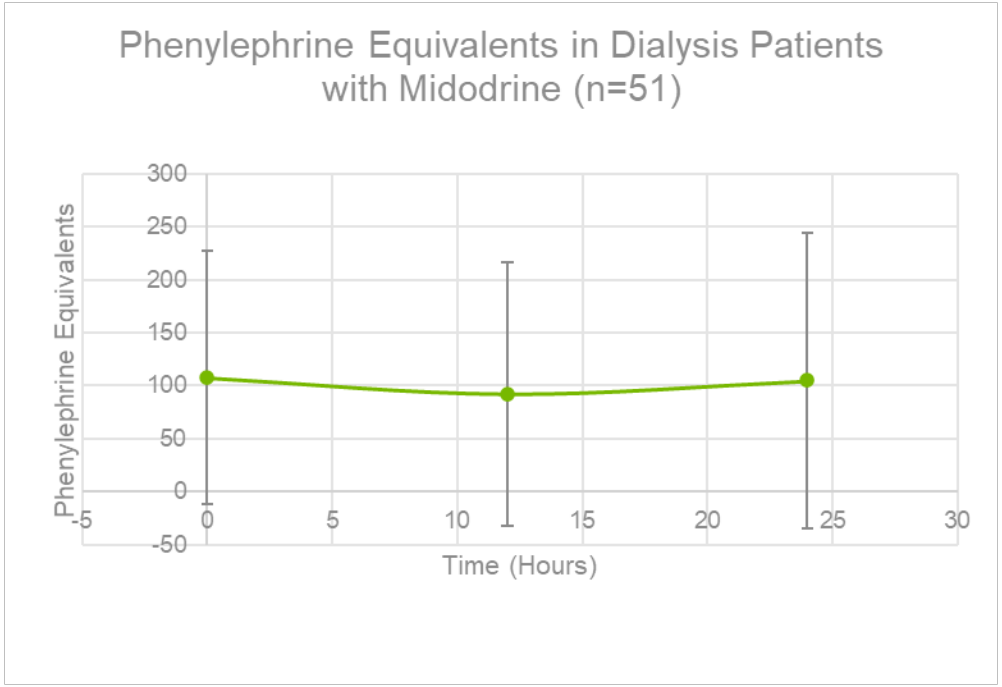
# Sub-analysis: Dialysis (n=51)




**Midodrine did not have a significant reduction in phenylephrine equivalents at 12 or 24 hours**

| Time | Phenylephrine Equivalents | P value |
|---|---|---|
| Baseline | 107.8 ± 119.4 | |
| 12 hours | 92.4 ± 124.0 | 0.099 |
| 24 hours | 104.8 ± 139.5 | 0.839 |

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# Sub-analysis: Dialysis

| | N=51 Midodrine | N=51 Control | P value |
|---|---|---|---|
| Age | 65.9 ± 10.2 | 67.1 ± 9.9 | 0.5316 |
| Max Daily Midodrine Dose (mg) | 35.5 ± 13.1 | NA | |
| Cirrhosis | 9 (17.7%) | 8 (15.7%) | 0.7930 |
| Concurrent Steroids | 25 (49.0%) | 21 (41.2%) | 0.3254 |
| Total Pressor Duration (days) | 6.45 ± 7.76 | 3.1 ± 2.6 | 0.0078 |
| Pressor Reinitiating | 2.1 ± 4.5 | 0.8 ± 1.0 | <0.001 |
| ICU/progressive care LOS (days) | 10.3 ± 9.3 | 8.2 ± 6.4 | 0.190 |
| Hospital LOS | 14.6 ± 12.6 | 12.7 ± 8.4 | 0.3760 |
| Hospital mortality | 8 (15.7%) | 8 (15.7%) | 1 |
| 30-day mortality | 26 (51.0%) | 17 (33.3%) | 0.0724 |

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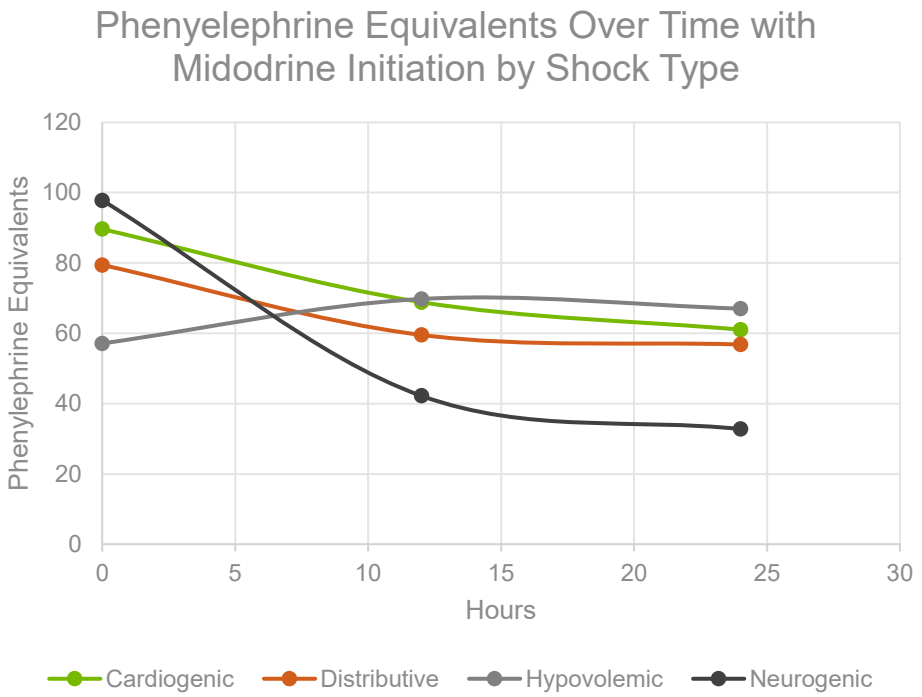
# Sub-analysis: Shock Type




**Vasopressor requirements trend down in all shock types except hypovolemic shock**

| | Baseline | 12 Hours | 24 Hours |
|---|---|---|---|
| Cardiogenic (n=25) | 89.7 ± 109.9 | 68.8 ± 118.5 | 61.0 ± 100.3 |
| Distributive (n=171) | 79.4 ± 95.9 | 59.5 ± 91.9 | 56.8 ± 100.3 |
| Hypovolemic (n=35) | 57.1 ± 72.8 | 69.8 ± 116.9 | 67.0 ± 133.4 |
| Neurogenic (n=9) | 97.8 ± 78.7 | 42.2 ± 47.6 | 32.8 ± 43.0 |

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# Sub-Analysis: Shock Type

| **Neurogenic** | **Hypovolemic** |
| --- | --- |
| No significant difference in any secondary outcome | No significant difference in any secondary outcome |
| **Distributive** | **Cardiogenic** |
| Several secondary outcomes disfavored midodrine use<br><br>• Vasopressor duration: (5.8 vs. 3.3, p<0.001)<br>• Vasopressor re-initiation: (1.9 vs. 0.8, p<0.001)<br>• 30-day mortality: (70 vs 25, p<0.001)<br>• Hospital LOS: (11.4 vs. 10.3, p=0.018) | Several secondary outcomes disfavored midodrine use<br><br>• Vasopressor duration: (8.4 vs. 2.9, p<0.001)<br>• 30-day mortality: (9 vs. 5, p=0.049) |

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# Discussion

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# Limitations

- Relatively small sample sizes resulting in large standard deviations
- Single health system
- Several confounders were included within the larger analysis
  - Steroids
  - Dialysis
  - Cirrhosis
- Midodrine was not always prescribed for the purpose of vasopressor tapering

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# Future Directions

- Increase sample sizes of sub-analysis groups
- Evaluation of COVID Patients
- Evaluation of midodrine initiated during a pause in vasopressor therapy
- Assessing provider prescribing practices

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# Conclusion

- Midodrine is associated with a significant reduction in phenylephrine equivalents at 24 hours
- Midodrine did not decrease the duration of vasopressors
- Midodrine may reduce ICU LOS
- Patients who may benefit: neurogenic shock

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# Acknowledgements


## Mentors

- Jim Roy, PharmD, BCCCPS
- Kris Howard, PharmD, AACC, BCCP
- Sarah Ferrell, PharmD, BCPPS


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# References


- Thongprayoon C, et. Al. Temporal trends in the utilization of vasopressors in intensive care units: an epidemiologic study. *BMC Pharmacology Toxicology.* 2016; 17 (19).
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