Review of adjunctive midodrine to facilitate weaning intravenous vasopressors in critically ill patients

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Review of adjunctive midodrine to facilitate weaning intravenous vasopressors in critically ill patients

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Florida Residency Conference (FRC)
Disclosure Statement

The following contributors have nothing to disclose regarding any financial or nonfinancial relationships with the products described, reviewed, or evaluated in this presentation:

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- Stephanie Palma Pharm.D., BCPS
Review the impact of adjunctive midodrine utilization to facilitate weaning intravenous (IV) vasopressors in a community hospital.
• IV vasopressors are utilized as mainstay therapy for shock in ICU
• Adverse effects:
  – Tachycardia
  – Local tissue necrosis
  – Gangrene if extravasation occurs
  – Bradycardia
  – Dysrhythmia
• Midodrine is an oral alpha-1 adrenergic agonist used as adjunctive therapy to wean off IV vasopressors
  – Decreases in ICU LOS and IV vasopressor rate
## Supporting Literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Study Design</th>
<th>Results</th>
</tr>
</thead>
</table>
| 2013 – Levine AR, et al | Midodrine was evaluated as adjunctive therapy to wean vasopressors | • Prospective, observational study  
Starting: 10 mg TID; Max: 40 mg TID  
20 patients included; 14 weaned in 24 hrs | Decreased vasopressor rate after initiating midodrine:  
-0.62 ± 1.40 mcg/min/hr compared to -2.20 ± 2.45 mcg/min/hr during the first four doses of midodrine (p=0.012) |
| 2016 – Whitson MR, et al | Evaluate the duration of vasopressor and ICU LOS with adjunctive midodrine therapy | • Retrospective, single-center, observational study  
140 patients: vasopressor alone  
135 patients: vasopressor + midodrine  
Starting dose: 10 mg TID; Max: 20 mg TID | • Decreased vasopressor duration: 8 days (vasopressor only) vs. 2.9 days (vasopressor + midodrine) (p<0.001)  
• Decreased ICU LOS: 9.4 days (vasopressor only) vs. 7.5 days (vasopressor + midodrine) (p=0.017) |
| 2019 – Rizvi, et al | Incidence of midodrine continuation upon ICU and hospital discharge and associated risks | • Single-center retrospective study  
1,010 patients included | • ICU discharge: 67% (672/1,010)  
• Hospital discharge: 34% (311/1,010)  
• 50% also prescribed antihypertensives  
• Shorter ICU LOS (7.5 ± 8.9 vs 10.6 ± 13.4 days) and reduced risk of in-hospital mortality (HR, 0.47 [95% CI, 0.32-0.70]; p < 0.001) |
Research Purpose

To assess how adjunctive midodrine is being utilized in our institution to wean off vasopressors.

To determine whether patients are being transitioned off midodrine when it is no longer warranted.
Research Setting

• Baptist Hospital of Miami
  – Non-profit community hospital
  – 728-bed
  – 40-bed ICU
Study Design

Approved by Baptist Hospital of Miami IRB

Phase I: Retrospective Chart Review
- Up to 100 patients between October 2018 - September 2019

Phase II: Prospective Chart Review
- Up to 100 patients between March - April 2020
- Pharmacist interventions

• Single center, biphasic study
Study Population

Inclusion

• Adults 18 years of age and older
• ICU admission
• Midodrine prescribed during admission in conjunction with IV vasopressor

Exclusion

• Midodrine is a pre-admission medication
• Pregnancy
Study Outcomes

Primary

• Time to vasopressor discontinuation after midodrine initiation
• Percentage of patients transitioned off midodrine at ICU and hospital discharge

Secondary

• Time from midodrine initiation to ICU discharge determination
• ICU LOS
• Time on vasopressor prior to initiation of midodrine
• Pharmacy interventions in phase II
• Duration of midodrine use
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>(age, gender, weight)</td>
</tr>
<tr>
<td>Dialysis status and urine output</td>
<td></td>
</tr>
<tr>
<td>APACHE IV score</td>
<td></td>
</tr>
<tr>
<td>Type of shock</td>
<td></td>
</tr>
<tr>
<td>Vasopressor starting rate, rate at midodrine initiation (mcg/kg/hr)</td>
<td></td>
</tr>
<tr>
<td>Average rate of vasopressor 24 hrs before midodrine initiation</td>
<td></td>
</tr>
<tr>
<td>Vasopressor duration before midodrine initiation</td>
<td></td>
</tr>
<tr>
<td>Duration of vasopressor with midodrine</td>
<td></td>
</tr>
<tr>
<td>Duration of vasopressor</td>
<td></td>
</tr>
<tr>
<td>Initial and maximum midodrine dose/frequency</td>
<td></td>
</tr>
<tr>
<td>Average daily dose of midodrine and average vasopressor rate (mcg/kg/hr)</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation and hydrocortisone utilization</td>
<td></td>
</tr>
<tr>
<td>ICU LOS</td>
<td></td>
</tr>
<tr>
<td>Reinstitution of vasopressor after discontinuation</td>
<td></td>
</tr>
<tr>
<td>Medication that counteracts midodrine (HR, BP, both)</td>
<td></td>
</tr>
<tr>
<td>Midodrine continued post ICU or post hospital discharge</td>
<td></td>
</tr>
<tr>
<td>Type of pharmacy intervention</td>
<td></td>
</tr>
</tbody>
</table>

**APACHE**: acute physiology and chronic health evaluation
Subject Selection – Phase I

73 patients reviewed

13 excluded

60 patients included

45/60 (75%) expired in ICU

15/60 (25%) discharged

Excluded:
- Midodrine and vasopressor not used concomitantly
- Midodrine x 1
Subject Selection – Phase II

64 patients reviewed

20 excluded

44 patients included

20/44 (45%) expired in ICU

16/44 (36%) discharged

8/44 (19%) remained hospitalized

Excluded:
- 13 patients:
  - No vasopressors
  - Midodrine was a home medication
  - Midodrine and vasopressor not used concomitantly
  - Midodrine x 1
- 7 patients:
  - Continuation of vasopressor and midodrine past study deadline
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Phase I (N=15)</th>
<th>Phase II (N=24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean, SD)</td>
<td>69.3 ± 16.3</td>
<td>67.6 ± 15.2</td>
<td>p = 0.751</td>
</tr>
<tr>
<td>Gender – male, n (%)</td>
<td>12 (80)</td>
<td>15 (63)</td>
<td>p = 0.305</td>
</tr>
<tr>
<td>APACHE IV Score (mean, SD)</td>
<td>61.9 ± 18.1</td>
<td>43.4 ± 15.2</td>
<td>p = 0.002</td>
</tr>
<tr>
<td>Type of shock, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distributive</td>
<td>11 (74)</td>
<td>21 (88)</td>
<td></td>
</tr>
<tr>
<td>Cardiogenic</td>
<td>2 (13)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Hypovolemic</td>
<td>2 (13)</td>
<td>2 (8)</td>
<td></td>
</tr>
<tr>
<td>Dialysis, n (%)</td>
<td>7 (47)</td>
<td>8 (33)</td>
<td>p = 0.505</td>
</tr>
<tr>
<td>Hydrocortisone utilization, n (%)</td>
<td>6 (40)</td>
<td>5 (21)</td>
<td>p = 0.277</td>
</tr>
<tr>
<td>Mechanical ventilation, n (%)</td>
<td>12 (80)</td>
<td>22 (92)</td>
<td>p = 0.354</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Vasopressor Information</th>
<th>Phase I (N=15)</th>
<th>Phase II (N=24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasopressor used, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>14 (93)</td>
<td>24 (100)</td>
<td>-</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>1 (7)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>3 (20)</td>
<td>3 (13)</td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td>6 (40)</td>
<td>7 (29)</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>2 (13)</td>
<td>3 (13)</td>
<td></td>
</tr>
<tr>
<td><strong>Midodrine initial dose, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mg TID</td>
<td>7 (47)</td>
<td>9 (38)</td>
<td>p = 0.739</td>
</tr>
<tr>
<td>10 mg TID</td>
<td>8 (53)</td>
<td>15 (63)</td>
<td></td>
</tr>
<tr>
<td><strong>Vasopressor rate in ICU</strong></td>
<td>9.6 ± 8.1</td>
<td>5.3 ± 3.4</td>
<td>p = 0.025</td>
</tr>
<tr>
<td><strong>Vasopressor rate at midodrine initiation</strong></td>
<td>8.6 ± 14.3</td>
<td>3.5 ± 3.2</td>
<td>p = 0.106</td>
</tr>
<tr>
<td><strong>(mcg/kg/min) (mean, SD)</strong></td>
<td>6.7 ± 11.0</td>
<td>2.7 ± 2.6</td>
<td>p = 0.096</td>
</tr>
</tbody>
</table>

*Norepinephrine equivalents*
Results: Primary Outcome

- Time to vasopressor discontinuation after midodrine initiation

<table>
<thead>
<tr>
<th></th>
<th>Phase I (N=15)</th>
<th>Phase II (N=24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days (mean, SD)</td>
<td>3 ± 5.2</td>
<td>4 ± 2.8</td>
<td>p = 0.832</td>
</tr>
</tbody>
</table>

- Percentage of patients transitioned off of midodrine

<table>
<thead>
<tr>
<th></th>
<th>Phase I (N=15)</th>
<th>Phase II (N=24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU Discharge, n (%)</td>
<td>6 (40)</td>
<td>19 (79)</td>
<td>p = 0.019</td>
</tr>
<tr>
<td>Hospital Discharge</td>
<td>9 (60)</td>
<td>22 (92)</td>
<td>p = 0.037</td>
</tr>
</tbody>
</table>
Results: Primary Outcome

Percentage of patients transitioned off of midodrine at hospital discharge

**Phase I**
- Yes: 60% (n=9)
- No: 40% (n=6)

**Reasons**
- Home with hospice (2)
- Transferred to other hospital (2)
- Transferred to long-term acute care (3)

**Phase II**
- Yes: 92% (n=22)
- No: 8% (n=2)

**Reasons**
- Transferred to other hospital
- Home with hospice
## Results: Secondary Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Phase I (N=15)</th>
<th>Phase II (N=24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from midodrine initiation to ICU discharge, days (mean, SD)</td>
<td>5 ± 6.7</td>
<td>12 ± 6.1</td>
<td>p = 0.002</td>
</tr>
<tr>
<td>ICU LOS, days (mean, SD)</td>
<td>12 ± 8.8</td>
<td>23 ± 11.9</td>
<td>p = 0.006</td>
</tr>
<tr>
<td>Time on vasopressor prior to initiation of midodrine, days (mean, SD)</td>
<td>5 ± 6.1</td>
<td>4 ± 2.8</td>
<td>p = 0.587</td>
</tr>
<tr>
<td>Midodrine duration, days (mean, SD)</td>
<td>12 ± 8.8</td>
<td>9 ± 8.3</td>
<td>p = 0.267</td>
</tr>
<tr>
<td>Pharmacy interventions in phase II, n</td>
<td></td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Taper midodrine</td>
<td>-</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Discontinue midodrine</td>
<td>-</td>
<td>14</td>
<td>-</td>
</tr>
</tbody>
</table>
Discussion

• Vasopressors were discontinued sooner in phase I (3 days) vs. phase II (4 days) after midodrine initiation
  – Average vasopressor duration was 8 days in both phases
• Patients in phase I were on vasopressors longer prior to midodrine initiation
  – Midodrine continued longer in phase I (12 days) vs. phase II (9 days)
• ICU LOS was shorter in phase I (12 days) vs. phase II (23 days)
  – Causes unrelated to vasopressor utilization
  – Mortality rate was higher in phase I (75%) vs. phase II (45%)
• Pharmacist involvement optimized midodrine therapy
Study Limitations

- Critically ill patients were included in phase I based on ICD-10 codes, which may have limited sample size.
- Phase I was retrospective and pharmacist interventions were not calculated.
- Limited sample size in phase II.
- Phase II was conducted during COVID-19 pandemic.
Conclusion

Midodrine was initiated later in phase I and continued for longer compared to phase II.

Due to pharmacist interventions in phase II, inappropriate use of midodrine was reduced at ICU/hospital discharge.

Future studies are necessary to solidify this correlation in our institution.
Which of the following is the role of midodrine in weaning off vasopressors?

A. Decrease blood pressure to maintain ACC/AHA blood pressure goal while in the ICU
B. Increase IV vasopressor rate to facilitate weaning
C. Increase adherence rates of anti-hypertensive medications once discharged
D. Decrease IV vasopressor rate, complications and ICU length of stay
Acknowledgements

• Heidi Clarke Pharm.D., BCCCP
• Payal Patel Pharm.D., BCCCP
• Radhan Gopalani Pharm.D., BCPS
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