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Impact of Midodrine on Optimization of β-blocker Therapy in Patients with Heart Failure with Reduced Ejection Fraction

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ABSTRACT

Introduction: Midodrine, an α-adrenergic agonist approved for orthostatic hypotension, is used off-label for hypotension in patients with heart failure with reduced ejection fraction (HFrEF). However, its prevalence, clinical outcomes, and risks in HFrEF remain unclear. Theoretically, adding midodrine to HFrEF patients' medication regimens may facilitate up-titration of guideline-directed medical therapy (GDMT) by attenuating its corresponding hypotensive effects. This study aims to assess the concurrent use of midodrine and β-blockers in patients with HFrEF to allow the initiation or up-titration of GDMT.

Methods: This was a multisite, retrospective chart review of adult patients with HFrEF who received concomitant treatment with midodrine and a β-blocker from March to June 2022. Patients were excluded if they were pregnant, had a left ventricular ejection fraction (LVEF) ≧ 50%, or received concomitant therapy for less than 48 hours. Primary outcomes included tolerance of β-blocker initiation and up-titration with midodrine. Secondary outcomes included initiation and continuation of midodrine and β-blockers or additional GDMT upon discharge.

Results: Twenty-six patients were included. All patients on midodrine were initiated on β -blockers, and 73% (*n* = 19) tolerated β-blocker dose titration. An improvement in mean systolic blood pressure (SBP) from 104 mmHg to 112 mmHg was observed. Nineteen (73%) patients were discharged on midodrine and β-blockers, while 7 (27%) patients were discharged on β-blockers alone.

Discussion: The initiation of midodrine improved mean SBP and enhanced tolerability of β-blockers in HFrEF patients. Further studies with larger sample sizes are necessary to evaluate midodrine's long-term risks and benefits in HFrEF.

Keywords: Midodrine, Heart Failure, HF, GDMT, Beta-blockers

INTRODUCTION

Optimizing guideline-directed medical therapy (GDMT) plays a central role in the management of heart failure with reduced ejection fraction (HFrEF). This therapy includes the use of β-blockers, angiotensin receptor-neprilysin inhibitors (ARNi), angiotensin-converting enzyme inhibitors (ACEi) or angiotensin (II) receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRA), and sodium-glucose-cotransporter-2 inhibitors (SGLT2i) to improve patient outcomes (Heidenreich et al., 2022). It is important to note that these therapies can potentially induce hypotension. Consequently, many patients with HFrEF face challenges

in tolerating these medications due to pre-existing hypotension or hypotension induced by the medications themselves (Al Turk et al., 2017). Hypotension is a primary cause of treatment failure for patients on β-blocker therapy.

Midodrine, an approved peripheral α-adrenergic agonist, is primarily indicated for the treatment of orthostatic hypotension. However, its off-label use extends to various conditions where the management or prevention of hypotension is desired (Gutman & Wilson, 2017). Nevertheless, midodrine's specific risks and benefits in patients with HFrEF are not yet well established. Few studies and cases have explored midodrine's potential role in treating heart failure (HF). In one study, adding midodrine increased mean systolic blood pressure (SBP) and improved tolerability of β-blockers (Vijayaraghavan et al., 2020). Similarly, in a case series of four patients with hypotension, midodrine facilitated the initiation of GDMT with clinical improvements (Shiu et al., 2022).

Overall, these studies suggest that midodrine may improve hemodynamic parameters and facilitate symptom management in patients with HF experiencing hypotension-related challenges while optimizing medical therapy. The purpose of this study was to investigate the concurrent use of midodrine and β-blockers in patients with HFrEF. This research aims to fill the existing knowledge gap regarding the utilization of midodrine in conjunction with β-blockers to improve the management of HFrEF and optimize GDMT strategies.

METHODS

This was a retrospective, observational, multi-site electronic health record review. Adults hospitalized with HFrEF concurrently receiving β-blockers and midodrine from March 2022 to June 2022 were included. Patients with a left ventricular ejection fraction (LVEF) greater than or equal to 50%, patients who were pregnant, and patients on concomitant therapy with a β-blocker and midodrine for less than 48 hours were excluded. Patient information was obtained through an informatics system report, and the patient list was de-identified using Microsoft Excel. Descriptive statistics were utilized for data analysis.

The primary outcomes included the number of patients who tolerated initiation and up-titration of β-blockers due to midodrine treatment. Secondary outcomes included the number of patients newly initiated on midodrine and β-blockers who were prescribed that regimen upon discharge and the number of patients newly initiated on midodrine and GDMT (ACE inhibitors, ARBs, ARNi, MRA or SGLT2i) who were prescribed that regimen upon discharge. Data collection included age, gender, LVEF, New York Heart Association (NYHA) classification, midodrine average daily dose, heart rate, blood pressure, creatinine clearance (CrCl), concomitant use of GDMT and inotropic agents, level of patient care at the time of midodrine initiation, change in vital signs after midodrine initiation, hospital length of stay (LOS), and 30-day readmission rate. Descriptive statistics were utilized for the primary and secondary outcomes.

RESULTS

During the study period, 160 patients with HF received concomitant midodrine and β-blocker therapy within the health system. The final analysis included 26 patients who met the inclusion criteria (Figure 1). The study patients exhibited a mean LVEF of 30% (*SD* ± 8.86), with the majority falling into HF NYHA class II and III. The mean midodrine dose was 20 mg (*SD* ± 9.90) per day, the median hospital LOS was 11.5 days (IQR 9), and 19% (*n* = 5) of patients experienced a 30-day hospital readmission (Table 1).

All 26 patients in the study tolerated initiation of β-blockers, and 73% (*n* = 19) tolerated the β-blocker therapy dose escalation (Table 2). The majority of the patients were initiated on metoprolol (58%), followed by carvedilol (23%) and

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Figure 1

Patient Screening and Selection

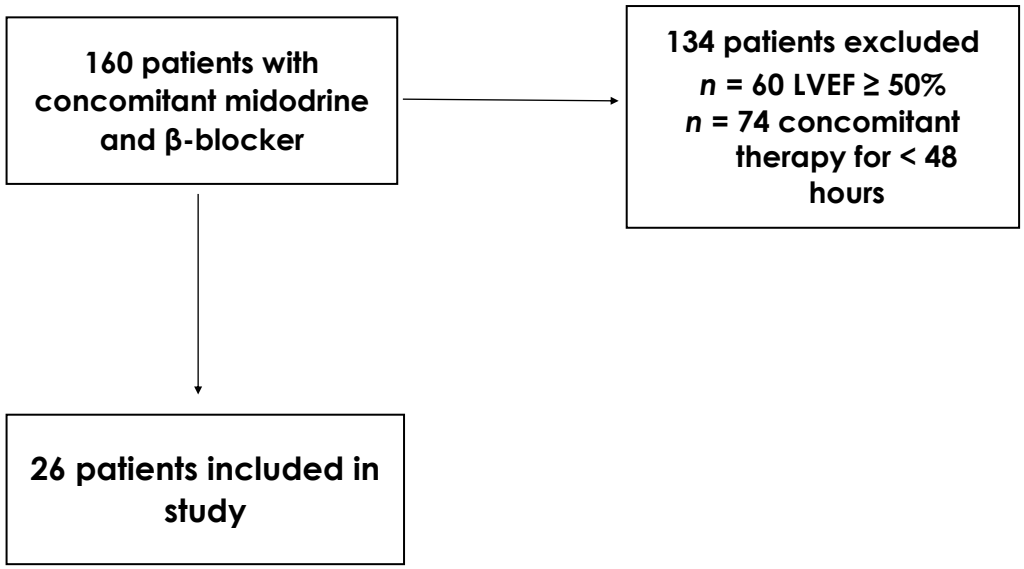

Table 1

*Baseline Characteristics (*N = *26)*

Characteristics	
Age, years, mean (*SD*)	74 (10.9)
Gender—male, *n* (%)	14 (53)
Comorbidities	
Hypertension, *n* (%)	16 (61)
Diabetes mellitus, *n* (%)	12 (46)
Ventricular failure, *n* (%)	2 (7)
Atrial fibrillation, *n* (%)	12 (46)
ESRD on HD, *n* (%)	5 (19)
LVEF, mean (*SD*)	30 (8.86)
NYHA Class	
Class II, *n* (%)	10 (38)
Class III, *n* (%)	15 (57)
Class IV, *n* (%)	1 (3)
NT-proBNP, pg/mL, median (IQR)	9287 (18747)
Midodrine daily dose, mean (*SD*)	20 (9.90)
Hospital LOS, days, median (IQR)	11.5 (9)
30-day hospital readmission, *n* (%)	5 (19)

Table 2

Primary Outcomes

Primary Outcomes	*n* (%)
Patients who tolerated initiation of β-blockers	26 (100)
Patients who tolerated up-titration of β-blockers	19 (73)

bisoprolol (19%). The mean heart rate of individuals included in the study was 90 beats per minute (bpm), which remained stable at 86 bpm with the initiation of midodrine. The mean SBP improved from 104 mmHg to 112 mmHg after midodrine initiation, and the mean diastolic blood pressure was maintained from 65 mmHg to 63 mmHg (Figure 2).

There were 73% (*n* = 19) of patients discharged on concomitant midodrine and β-blockers, whereas 19% (*n* = 5) of patients were discharged with additional GDMT (Table 3). Notably, 31% (*n* = 8) of patients were discharged on digoxin, 19% (*n* = 5) were discharged on an MRA, and 11% (*n* = 3) were discharged on a SGLT2i (Table 4). Moreover, 11 patients (42%) were discharged on two or more of the four pillars of GDMT in HFrEF (Table 5). Of note, five patients were readmitted within 30 days, four of which were readmitted due to a HF exacerbation (Table 1).

DISCUSSION

This study demonstrated that initiating midodrine in patients with HFrEF facilitated the optimization of GDMT, primarily involving the use of β-blockers. These findings contribute to the growing body of evidence supporting the role of midodrine in enhancing the tolerability and effectiveness of β-blockers in HFrEF patients. The patient population included in this study consisted of individuals with HFrEF and NYHA classification of II or greater. Additionally, approximately half of the participants were male, with a mean age of 74 (Table 1).

The results of this study align with previous findings that support the positive impact of initiating midodrine in patients with HF. In a study by Vijayaraghavan et al. (2020), 60 patients intolerant to β-blocker, ARNi, and MRA therapy with SBP less than 95 mmHg were initiated on midodrine. The mean midodrine dose was 20.7 mg daily, and the mean SBP improved by 8 mmHg (± 4). Approximately 94% of patients tolerated initiation of GDMT with concomitant midodrine therapy. Notably, 75% (*n* = 45) of patients were successfully initiated on β-blockers, 50% (*n* = 30) on an ARNi, and 33% (*n* = 20) on an MRA (Vijayaraghavan et al., 2020).

In a report of a 56-year-old male with an ejection fraction of 35%, a mean blood pressure of 70/52 mmHg, and intolerance to carvedilol and losartan, the initiation of midodrine allowed for the reintroduction of both GDMT agents. The re-initiation of GDMT was accompanied by an increase in the EF to 58%. Likewise, in a 58-year-old female with HFrEF (LVEF 18%), GDMT with losartan and carvedilol resumed after two months of midodrine therapy. This led to an increase in her LVEF to 28%. Midodrine therapy also led to the initiation of metoprolol succinate, spironolactone, and losartan in a 61-year-old patient following vasopressor requirement during hospitalization. Lastly, in a 57-year-old patient with a history of frequent HF hospitalizations, midodrine therapy facilitated the initiation of carvedilol, sacubitril-valsartan, and spironolactone. With the initiation of GDMT, the patient experienced a reduction in HF hospitalizations and an increase in LVEF from 31 to 49% (Shiu et al., 2022).

By expanding upon the current observational data, our findings support the

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Figure 2

Average Change in Vital Signs with Initiation of Midodrine

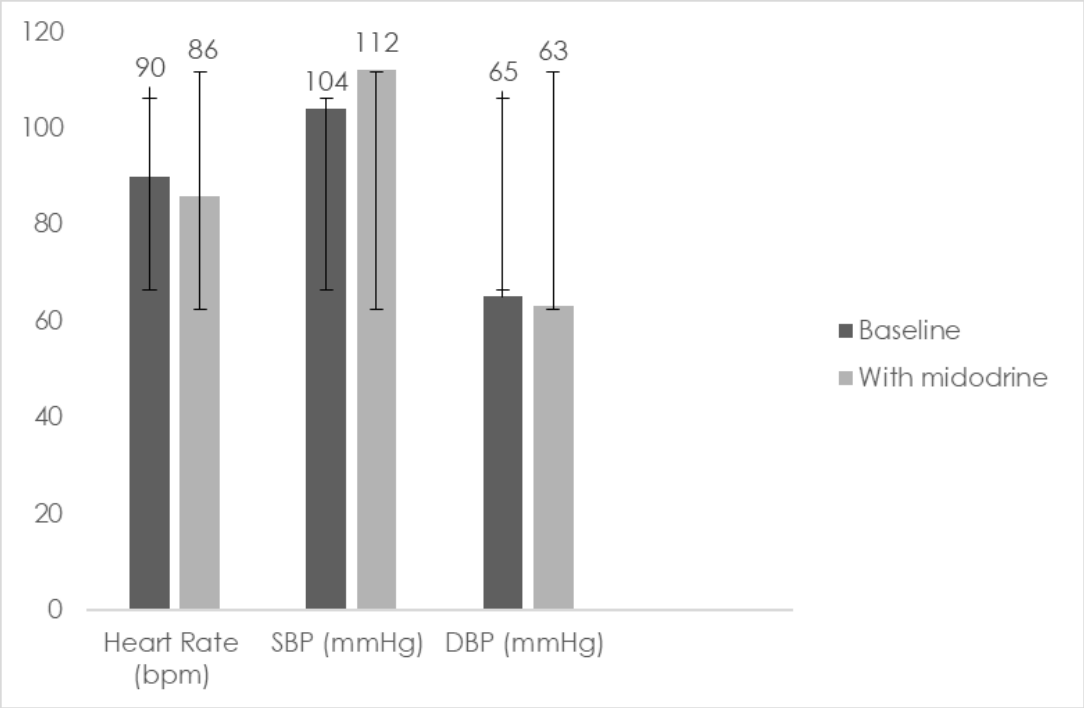

Table 3

Secondary Outcomes

Secondary Outcomes	*n* (%)
Patients discharged on midodrine and β-blockers	19 (73)
Patients discharged on midodrine and additional GDMT, including ACEi/ARBs, ARNi, MRA, or SGLT2i	5 (19)

Table 4

Concomitant HF Medications

Medication	*n* (%)
ACEi/ ARB/ARNi	2 (8)
β-blocker*	26 (100)
MRA	5 (19)
SGLT2i	3 (12)
Digoxin	8 (31)
Dobutamine	1 (4)

Note. *7 patients discharged on β-blockers alone

Table 5

Patients on GDMT

GDMT	*n* (%)
β-blocker + ACEi/ARB/ARNi	3 (12)
β-blocker + MRA	4 (15)
β-blocker + SGLT2i	1 (4)
β-blocker + ACEi/ARB/ ARNi + SGLT2i	1 (4)
β-blocker + ACEi/ARB/ARNi + MRA	1 (4)
β-blocker + ACEi/ARB/ARNi+ MRA + SGLT2i	1 (4)

evidence that a-agonists may play a beneficial role in improving the tolerability of GDMT in patients with HFrEF. However, it is essential to consider the current study's limitations, including its retrospective nature, which introduces inherent limitations. The small sample size, potential inaccuracies in medical record documentation, and data extraction also contribute to the study's limitations. To further evaluate the long-term risks and benefits of midodrine in patients with HFrEF, future prospective studies with larger sample sizes and a more diverse patient population are warranted. Such studies will provide a more comprehensive understanding of the potential benefits and risks associated with midodrine therapy in HFrEF patients and contribute to the optimization of GDMT strategies.

CONCLUSION

In conclusion, this study demonstrated that initiating midodrine in patients with HFrEF led to notable improvements in mean SBP and enhanced the tolerability of β-blockers. The overall findings suggest that midodrine may be a valuable adjunct therapy in the management of HFrEF, especially in patients who experience difficulties tolerating β-blockers due to pre-existing or drug-induced hypotension. Further studies are necessary to evaluate the long-term risks and benefits of midodrine in patients with HFrEF.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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REFERENCES

Al Turk, A. A., Odanovic, N. R., Waller, A. H., & Mazza, V. J. (2017). Midodrine and pyridostigmine; Novelties in heart failure therapy. *Journal of Cardiovascular Disease Research*, *8*(4), 104–107. http://www.jcdronline.org/paper.php?slug=midodrine-and-pyridostigmine-novelties-in-heart-failure-therapy

Gutman, L. B., & Wilson, B. J. (2017). The role of midodrine for hypotension outside of the intensive care unit. *Journal of Population Therapeutics and Clinical Pharmacology*, *24*(3), e45–e50. https://pubmed.ncbi.nlm.nih.gov/28873293/

Heidenreich, P. A., Bozkurt, B., Aguilar, D., Allen, L. A., Byun, J. J., Colvin, M. M., Deswal, A., Drazner, M. H., Dunlay, S. M., Evers, L. R., Fang, J. C., Fedson, S. E., Fonarow, G. C., Hayek, S. S., Hernandez, A. F., Khazanie, P., Kittleson, M. M., Lee, C. S., Link, M. S., … Yancy, C. W. (2022). 2022 AHA/ACC/HFSA guideline for the management of heart failure: Executive summary: A report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*, *145*(18), e876–e894. https://doi.org/10.1161/CIR.0000000000001062

Shiu, P., Grewal, G. S., & Kozik, T. M. (2022). Midodrine to optimize heart failure therapy in patients with concurrent hypotension. *SAGE Open Medical Case Reports*, *10*, 1–5. https://doi.org/10.1177/2050313X221100400

Vijayaraghavan, K., Little, D., Mercer, T., Querrey, T., Wilmowski, S., Win, A., Cherukuri, G., & Byrne, T. (2020). Midodrine as a bridge to enable use of life enhancing therapies in chronic heart failure. *Journal of Cardiac Failure*, 26 (10), S59. https://doi.org/10.1016/j.cardfail.2020.09.175