



## Efficacy of Midodrine on Hemodynamics

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### ABSTRACT

**Objectives:** To assess the use of Midodrine among patients with orthostatic hypotension and withdrawal vasopressin in King Abdulaziz Medical City (KAMC), demonstrate the effectiveness and safety of Midodrine and detect side effects to provide clear evidence of the efficacy and safety of the drug. **Methods:** A retrospective cohort study was done in King Abdulaziz Medical City in Riyadh (Saudi Arabia). The study targeted adult patients who suffered from hypotension between January 2015 and January 2018. The data was extracted using the BESTCare system. **Result:** A total of 173 patients were included (55.5% male and 44.5% female). The mean age of the study participants was  $67.34 \pm 16.0$  years. The differences in patients' parameters before and after midodrine administration were detected and analyzed. The mean difference in hemoglobin (g/l) level was significantly changed before ( $94.97 \pm 21.9$ ) and after ( $90.84 \pm 20.4$ ) the use of Midodrine ( $p=0.031$ ). However, there were no significant changes in the level of the other parameters before and after the use of Midodrine. The mean dose of Midodrine was 5.3 mg, with mean treatment duration of 41.5 days, and mean hospitalization of 28.7 days. For the medication history, 8% of patients were on beta-blockers ( $n=97$ ), 5% were on diuretics ( $n=64$ ), and 2% were on calcium channel blockers ( $n=19$ ). **Conclusion:** Our data suggest that the administration of Midodrine does not affect patients' hemodynamics significantly; however, it has a notable effect on decreasing hemoglobin levels.

**Keywords:** Hemodynamics, Midodrine, Efficacy, Orthostatic hypotension

**Abbreviations:** HR: Heart Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure; Scr: Serum creatinine; INR: International Normalized Ratio; Hgb: Hemoglobin; RRI: Renal Resistive Index; CO: Cardiac Output; PRA: Plasma Rennin Activity; OH: Orthostatic hypotension; US FDA: United States Food and Drug Administration; USA: United States of America; CI: Confidence Interval; ICU: Intensive Care Unit; BMI: Body Mass Index

### INTRODUCTION

Midodrine is a vasopressor medication. It is a sympathomimetic drug that acts by stimulating alpha-receptors, which both noradrenaline and adrenaline work on. Midodrine is used to manage hypotension and relieve its associated symptoms, such as dizziness and fatigue, by increasing the blood pressure through constricting the blood vessels [1-4]. It is an orally administered drug. Following administration, it metabolizes to an active form "Desglymidodrine" which binds to noradrenaline receptors [5].

Midodrine can also be used for other conditions, such as improving hemodynamics like Mean arterial blood pressure (MAP), Renal resistive index (RRI), and Cardiac output (CO) in ascites and cirrhosis [1]. A study was conducted in 2011, aimed to assess the effect of Midodrine on the hemodynamics of patients with cirrhosis. In this study, Midodrine significantly increased the Mean arterial blood pressure (MAP) and decreased the Cardiac output (CO), Plasma rennin activity (PRA), and the Renal resistive index (RRI) in cirrhotic patients with ascites [1]. The results showed that for pretreatment, MAP in group I ( $93.4 \pm 4.7$  vs.  $90.6 \pm 10.1$ ) and group II ( $84.7 \pm 3.19$  vs.  $84.4 \pm 11.9$ ) and CO in group I ( $6438.2 \pm 508.8$  vs.  $6400 \pm 1300$ ) and group II ( $6833.2 \pm 425.14$  vs.  $6800 \pm 1400$ ) values and the PRA result was  $2.1 \pm 1.12$  [1]. Kalambokis, et al. evaluated the effect of administering 10 mg Midodrine for one week in non-azotemic cirrhotic patients with and without ascites [6]. It was associated with a significant increase in the MAP ( $p < 0.05$ ) and systemic vascular resistance ( $p < 0.01$ ) [6]. Also, it was associated with a significant decrease in the CO ( $p < 0.05$ ) and HR ( $p < 0.01$ ) [6].

Although Midodrine tolerability is considered safe in most patients, few side effects were noticed, including piloerection, general paresthesia or pruritus, chills, and urinary retention in a small percentage of people [7]. Midodrine does not affect insulin and uric acid levels nor serum lipid profile [7]. It is contraindicated in people with severe heart diseases, acute kidney diseases, urinary retention, and thyrotoxicosis. Also, it should not be used in people with excessive supine hypertension [8]. Many studies demonstrated that acute oral administration of Midodrine is related to a significant increase in systemic hemodynamics in patients with ascites, renal perfusion, or chronic hypotension [5,9].

Orthostatic hypotension (OH) is a chronic neurodegenerative disorder caused by the dropping of systolic blood pressure of at least 20 mmHg, or diastolic blood pressure of at least 10 mmHg when the patient stands up. This condition can also affect the quality of life. It results in cerebral hypoperfusion symptoms such as dizziness and blurring of vision. It also may result in substantial morbidity and mortality from associated fainting and falls. Orthostatic hypotension usually affects older adults and may increase with age. The percentage can reach up to 16.2% in people above 65 years old [7,10,11].

The goal of therapy in orthostatic hypotension is to improve symptoms and prevent falls. Stoppage of medications, such as (diuretics,  $\alpha$ -1 adrenergic antagonists, and tricyclic antidepressants) may cause OH. The use of compression garments and drinking sufficient amounts of water can be used as management strategies for orthostatic hypotension [10]. If the previous treatments did not work, a switch to medical treatment is needed. According to the European Federation of Neurological Societies, fludrocortisone, a synthetic mineralocorticoid analog, considered the first-line treatment for OH. However, it is not approved for OH by US FDA due to adverse effects such as congestive heart failure, while Midodrine, a prodrug for the active metabolite Desglymidodrine  $\alpha$ -1 agonist, is the only US FDA approved drug to manage OH and its clinical symptoms. It may cause hyperlipidemia and hyperglycemia [7,10].

However, in 2017, a retrospective cohort study conducted in the USA, which evaluated the relative safety of Midodrine and fludrocortisone found that the initiation of Midodrine for patients with OH was associated with a significantly lower incidence of hospitalization compared to fludrocortisone (95% CI, 1.02-1.4) [10].

A placebo-controlled, randomized, multicenter study evaluated the effectiveness of Midodrine in the treatment of OH; the study reported that Midodrine has no related incidence of supine hypertension. It can reduce the recurrence of blood pressure drop after standing up, the severity of falls and syncope, and cause an increase in blood pressure and vascular tone ( $p = 0.0131$ ) [11]. Also, a systematic review evaluated the role of Midodrine in patients with recurrent reflex syncope, and symptomatic orthostatic hypotension showed that Midodrine improved the outcomes in patients with these conditions [12]. On the other hand, a multicenter, randomized, placebo-controlled trial conducted in the USA and Australia assessed the use of Midodrine as adjunctive therapy in reducing the duration of therapy and hospitalization. Midodrine use reduced the OH levels; it increased the standing systolic blood pressure by 22 mmHg (28%,  $p < 0.001$  versus placebo) [8]. They suggested that Midodrine improves clinical outcomes in patients with secondary or orthostatic hypotension. The safety and effectiveness of Midodrine among the Saudi population is not studied yet. This study aimed to evaluate the effect of Midodrine use on the hemodynamic parameters of non-cirrhotic Saudi patients.

## METHODS

### Study Design

Observational retrospective cohort study.

**Ethics Approval**

The study was approved by the Research Ethics Committee of King Abdullah International Medical Research Center.

**Study Sites**

This study will be conducted at King Abdulaziz Medical City (KAMC), a tertiary academic hospital located in Riyadh, Kingdom of Saudi Arabia. The hospital has expanded over the years with a bed capacity that now has reached 1501. The study targeted adult patients who suffer from hypotension between January 2015 and January 2018 with the exclusion of patients with an accompanying case of liver cirrhosis

**Data Collection**

Data collection will be done using (Best care) electronic health records. Also, pharmacy records will be reviewed for medication history. Patients who are admitted to cardiac wards will be reviewed using the Apollo system.

**Collected Data**

- Age
- Gender
- Weight
- BMI
- Physical assessment and laboratory findings (before and after starting the use of midodrine)
- Medical history
- Medication history
- Etiology of OH
- Patient's setting when use midodrine
- The prescription of Midodrine for hypotension
- Dose of Midodrine
- Length of treatment
- Occurrence of side effects of midodrine
- Severity of side effect
- Occurrence of serious adverse events
- Total length of hospitalization

**Data Analysis**

The data were entered and compiled by using Microsoft Excel 2010 and were analyzed by using the statistical software SPSS 22.0 version (IBM, USA). In the present study, data were analyzed with the use of necessary statistical methods to achieve the objectives of the study. The quantitative data were expressed in Mean and Standard Deviation. The qualitative data were expressed as frequency and percentages. The mean comparison of before and after measurement of the various clinical variables was made by using the paired t-test. A  $p < 0.05$  was considered statistically significant.

**RESULTS**

A total of 173 patients were included in this study. 96 (55.5%) were male and 77 (44.5%) were female. The mean age of the study participants was  $67.34 \pm 16.0$  (20-98) years and weight  $70.2 \pm 18.4$  (Range: 38-150) Kgs (Table 1). Out of the study participants, 58.4% of them were ICU admitted patients, while 15.6% were non-ICU (Table 2).

The differences in patient's parameters (HR, SBP, DBP, MAP, Scr, INR, Hgb) before and after the midodrine administration were detected and analyzed (Table 3). The mean difference in hemoglobin level was significantly changed

(94.97 g/l  $\pm$  21.9 g/l before) (90.84 g/l  $\pm$  20.4 g/l after) (p=0.031). However, there were no significant changes in the level of the other parameters before and after the use of midodrine.

The mean dose of midodrine was 5.3 mg, with mean treatment duration of 41.5 days, and mean hospitalization of 28.7 days (Table 4).

### Comorbidities

The most prevalent comorbidity identified was Diabetes mellitus, which was found in 17% of the patients (n=113) followed by hypertension (17% [n=111]), Heart diseases (15% [n=99]), Kidney diseases (13% [n=89]), Thyrotoxicosis (3% [n=19]), Liver diseases (2% [n=12]), Psychiatric diseases (1% [n=9]), and Urinary retention (0.5% [n=3]). The complete list of comorbidities can be viewed in Figure 1.

### Medication History

When it comes to the medication history of the patients, 8% of the patients were on beta-blockers (n=97), 5% were on diuretics (n=64), and 2% were on calcium channel blockers (n=19) (Figure 2).

**Table 1 Distribution of the sample study according to the demographic data clinical variables (N=173)**

Socio-Demographic Variables	No. of Patients	Percentage (%)
<b>Gender</b>		
Male	96	55.5%
Female	77	44.5%
Age (in years) (n=172)*	67.3 $\pm$ 16.0 (Range: 20-98)	
Weight (in Kgs) (n=169)*	70.2 $\pm$ 18.4 (Range: 38-150)	
BMI (n=169)*	28.8 $\pm$ 14.0 (12-150)	

BMI: Body Mass Index; \*Missing value occurred

**Table 2 shows the participants distribution according to patient setting (N=173)**

Patient Setting (n=128)*	Frequency	Percentage (%)
ICU	101	58.4%
Non-ICU	27	15.6%

ICU: Intensive Care Unit; \*Missing value occurred

**Table 3 Showing the Paired Samples T-test result to test value and significance of differences between before and after of HR, SBP, DBP, MAP, Creatinine, INR, Hemoglobin of the study participants (N=173)**

Clinical Variables		No.	Mean	Std. D	t-test	p-value
Heart Rate (b\m)	Before	161	84.63	16.45	-0.979	0.329
	After	161	86.29	17.98		
Systolic BP (mmHg)	Before	166	110.2	22.47	0.357	0.721
	After	166	109.38	23.27		
Diastolic BP (mmHg)	Before	166	58.92	14.98	0.271	0.786
	After	166	58.51	14.35		
MAP (mmHg)	Before	86	70.65	13.51	-1.815	0.073
	After	86	73.93	16.23		
Creatinine (g\l)	Before	146	238.2	202.62	1.714	0.089
	After	146	212.63	182.52		
INR	Before	106	1.68	3.56	0.118	0.906
	After	106	1.42	0.965		
Hemoglobin (g\l)	Before	144	94.97	21.99	2.18	0.031*
	After	144	90.84	20.42		

BP: Blood Pressure; MAP: Mean Arterial Pressure; INR: International Normalized Ratio; \*p<0.05 Statistically significant

Table 4 Showing the Mean, Standard Deviation and Range of the Clinical Variables (N=175)

Clinical variables	Mean	Std. Dev	Range
Dose*	5.3	2.8	2-15
Length of Treatment*	41.5	79.1	3-777
Length of Hospitalization*	28.7	20.1	1-92

\*Missing value occurred

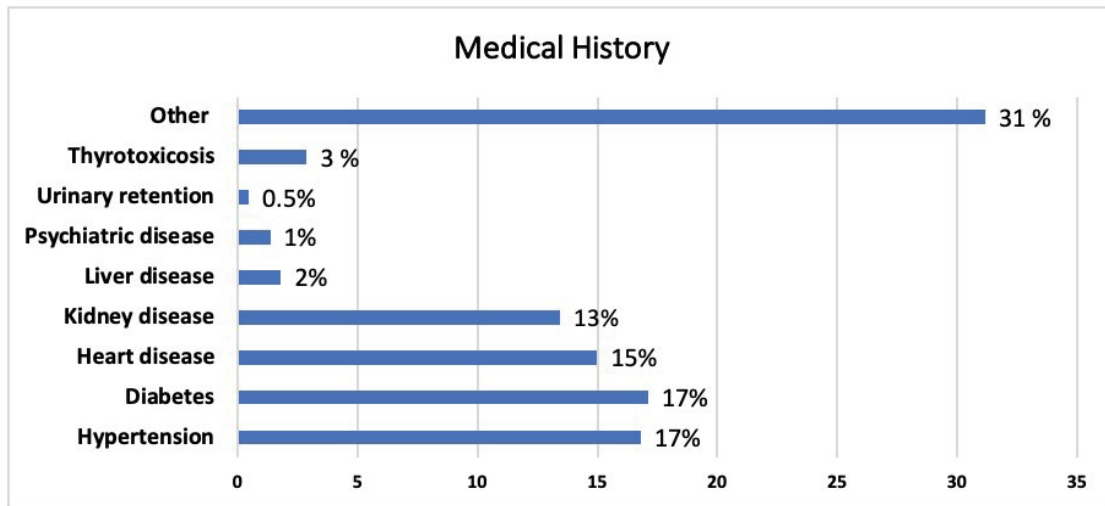


Figure 1 Complete list of comorbidities

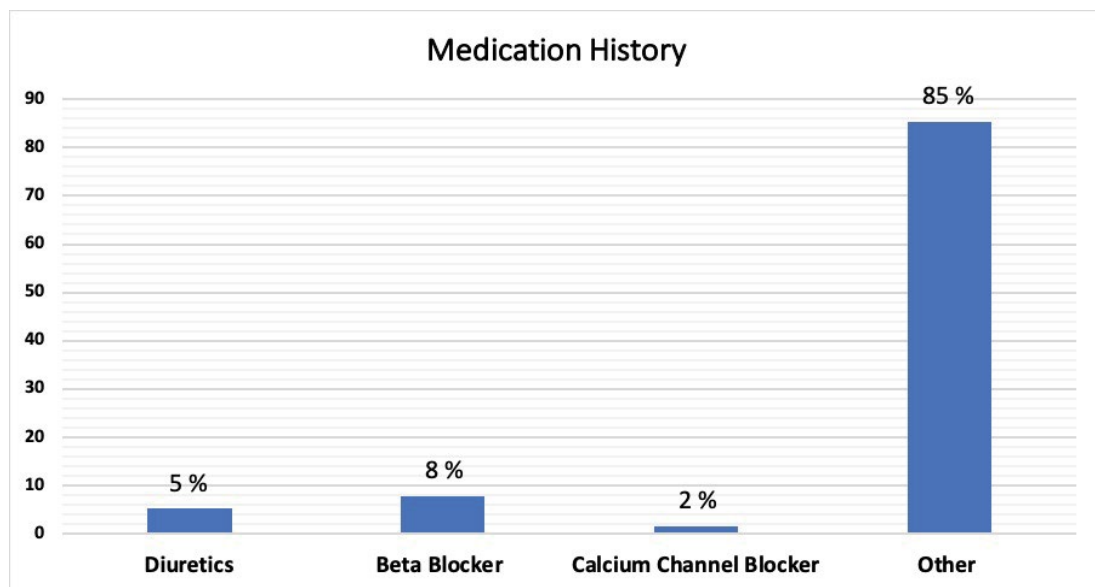


Figure 2 Medication history

### DISCUSSION

The mean differences in mean atrial pressure of the study participants before and after the administration of midodrine were not statistically significant. However, in a study conducted in mayo clinic, 2018, the use of midodrine was associated with a significant increase in median MAP within 24 hours after administration of midodrine ( $p < 0.01$ ) [13]. In another study conducted in China, the use of midodrine in hemodialysis patients was associated with a significant increase in the MAP during hemodialysis ( $79.5 \pm 4.9$  to  $85.0 \pm 5.1$  mmHg,  $p < 0.05$ ) [14].

In our study, the mean difference in hemoglobin level was significantly changed ( $94.97 \pm 21.9$  g/l before) ( $90.84 \pm 20.4$  g/l after) ( $p=0.031$ ), while there were no significant changes in the level of the HR, SBP, DBP, Scr, and INR of the study participants. In a systematic review and meta-analysis did by Parsaik, et al. in the USA, the study evaluated the efficacy and safety of midodrine in OH. They found that midodrine administration was significantly associated with a change in the standing SBP ( $p<0.001$ ). However, the mean change in SBP was 4.9 mmHg ( $p=0.65$ ) and the mean change in MAP from supine to standing was -1.7 mmHg ( $p=0.45$ ) [15].

The use of low and high doses of midodrine was associated with the same effect in the hemodynamic parameters. However, the only significant effect of the Midodrine administration was on the hemoglobin level.

### CONCLUSION

Our data suggest that the administration of oral Midodrine does not affect patients' hemodynamics significantly; however, it has a notable effect on decreasing hemoglobin levels.

### DECLARATIONS

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#### Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article..

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