

Midodrine for Prevention of Intradialytic Hypotension in High Risk Patients at a Tertiary Referral Hospital: A Retrospective Study

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Abstract

Background: Intradialytic hypotension (IDH) is the most common complication during hemodialysis procedure. Midodrine, an oral α -1 adrenergic agonist, is commonly used to prevent IDH. However, limited data is available to demonstrate midodrine effectiveness in prevention of IDH in high-risk hemodialysis patients. **Objective:** To describe the clinical outcomes of using midodrine in patients receiving hemodialysis concerning the incidence of IDH. Also, we aimed to explore the appropriate dose for midodrine use to prevent IDH. **Methodology** A retrospective cohort of adult with end-stage-renal failure. **Exposure:** Midodrine. **Outcomes measure:** IDH was defined as a decline in systolic blood pressure (SBP) by ≥ 20 mmHg or a decline in mean arterial pressure (MAP) by ≥ 10 mmHg during hemodialysis session. Recurrent IDH was defined as three or more episodes of IDH throughout a year of starting midodrine. **Analysis:** A descriptive analysis of the frequency of IDH and recurrent IDH. We also, compared the risk of recurrent IDH across various doses of midodrine use. **Result:** From a total of 68-screened patients' charts, 45 patients were included in the final analysis. 41.8% (n=28) of the study population had an IDH that required additional interventions to restore the SBP and MAP. IDH occurred in 68% (n=19, P=0.03) of patients with hypoalbuminemia. Recurrent IDH occurred in 36% (n=16) of the patients over their hemodialysis procedure. Incidence of treatment failure (57%, p= 0.02) and recurrent IDH (36%, p=0.04) were statistically significant in patients who received midodrine three time per week (57%) in comparison to those who received more than three days per week **Conclusion:** This exploratory study shows that a considerable proportion of patients receiving midodrine did not develop IDH or recurrent IDH. A long-term follow-up study with larger number of patients in comparison to the control group would be useful to evaluate the magnitude of efficacy of midodrine in hemodialysis patients with high risk for IDH. Moreover, a future prospective trial that focus on an important clinical outcomes such as cardiovascular events and mortality with midodrin is warranted.

Background

Intradialytic hypotension (IDH) is the most common complication that is well recognized during hemodialysis, it occurs in around 15% to 50% of hemodialysis patients⁽¹⁾. IDH is associated with a negative impact on health-related quality of life: because it requires an early termination of the hemodialysis session causing insufficient fluid removal, then increasing the cardiovascular morbidity and mortality⁽²⁾. The pathogenesis mechanism of IDH is very complex, but mainly results from an excessive rate of fluid removal than that required for achieving a rate for intravascular filling, which ends in causing an intravascular volume depletion⁽³⁾. There is no consensus definition of IDH, however, according to the Kidney Disease Outcomes Quality Initiative and European Best Practice Guidelines, IDH is defined as a decline in systolic blood pressure ≥ 20 mmHg or a decrease in a mean arterial pressure by 10 mmHg and associated with clinical events like abdominal pain, nausea, vomiting, muscle cramps, dizziness, fatigue, and restlessness^{(4), (5)}. Major factors that contribute to IDH are older age ≥ 65 years, female gender, predialysis systolic blood pressure < 100 mmHg, presence of diabetes mellitus, cardiovascular disease, using a peripheral vasodilator or short-acting antihypertensive medication(s), anemia, uremia, autonomic

or neuropathy dysfunction, hypoalbuminemia or poor nutritional status, higher dialysate temperature, or higher ultrafiltration volume ^{(5),(6)}. There are numerous therapeutic strategies that have been used to manage IDH with varied degrees of success, including placing the patient in the trendelenburg position, decreasing ultrafiltration rate, elevating dialysate calcium level, using bicarbonate-based dialysate, and giving boluses of intravenous fluids like isotonic saline and colloid solutions ^{(4),(5),(7)}. The third-line approach to manage and prevent IDH is using a pharmacological intervention including: Midodrine, Carnitine, or Sertraline ^{(4),(5),(8)}. Midodrine is an oral α -1 adrenergic agonist pro-drug with an active metabolite desglymidodrine that increases arteriolar and venous tone which causes a rise in standing, sitting, and supine systolic and diastolic blood pressure ⁽⁹⁾. It is effectively cleared by the hemodialysis with reducing in half-life to 1.4 hour in hemodialysis patient ⁽¹⁰⁾. The best data are from a systematic review of 10 literatures revealing that using 2.5 to 10 mg of midodrine given 15–30 minutes before the dialysis elevated the post-dialysis systolic and diastolic blood pressures by 12.4 mmHg and 7.3 mmHg above the values in controls, respectively, and that the nadir systolic and diastolic blood pressure was higher by 13.3 mmHg and 5.9 mmHg compared with the control group, respectively ⁽¹¹⁾. Midodrine (5 mg twice daily) showed a significant increase in mean arterial pressure among hemodialysis patients with chronic hypotension secondary to autonomic dysfunction as well ⁽¹²⁾. In most circumstances, the usual management of patients with a high risk of IDH requires a various of modalities to prevent IDH. However, more clinical studies are needed to validate the efficacy of one approach over any other ⁽⁵⁾. The objective of this study is to evaluate the efficacy of Midodrine for prevention of IDH in high-risk hemodialysis patients.

Methods

A descriptive retrospective cohort study was approved by the Institutional Review Board in January 2018. It was conducted at a tertiary care center in Riyadh. The medical and pharmacy data used in this study was retrieved from electronic health records for adult patients with end-stage renal disease on hemodialysis who were placed on midodrine. IDH was defined as a decline in SBP by ≥ 20 mmHg or a decline in MAP by ≥ 10 mmHg ⁽⁵⁾. Recurrent IDH was defined as three or more episodes of IDH throughout a year of starting midodrine. ⁽⁶⁾ The risk factors that contributed to IDH were identified through the following variables: patient's age, gender, body mass index ⁽¹³⁾, presence of diabetes mellitus, cardiovascular disease, iron deficiency anemia ⁽¹⁴⁾, hypoalbuminemia ⁽⁸⁾, neuropathy dysfunction, and uremia ⁽¹⁵⁾. Dose and frequency of midodrine were recorded for each hemodialysis session.

Statistical analyses:

Statistical analyses was performed by using SPSS 19.0 software (IBM, NY, USA). Categorical data was expressed as percentage and analyzed with chi-square test. Continuous data was expressed as mean \pm SD and compared by the Student's t-test. All statistical assessments was 2-tailed and the level of significance was set to be at $p = 0.05$. Multiple logistic regression was applied to find the association

between using Midodrine with the multiple independent variables such as systolic and diastolic blood pressure, treatment failure, and IDH recurrence.

Results

From a total 68 patients' charts were screened, 23 were excluded due to insufficient patients information in 7 patients and 2 patients were on peritoneal dialysis, whereas 14 more patients were excluded due to loss of follow up. The remaining 45 patients were eligible for the final analysis. Overall, IDH was recorded in 28 HD patients (41.8%) eventually those patients required an additional interventions to restore the SBP and MAP, such as placing the patient in trendelenburg position, decreasing the hemodialysis ultrafiltration rate, giving boluses of intravenous 0.9% normal saline or 20% Human albumin solutions, and some of patients were demanded an early termination of the hemodialysis session. In term of recurrent IDH, it was occurred in 16 HD patients (36%). The vast majority of patients had a combined risk factors of IDH. There are summarized in table 1.

Table 1: Risk Factors of Intradialysis Hypotension

Risk Factor	Total N=45 N (%)
Female gender	24 (53.3%)
Elderly	23 (51.11%)
Diabetes mellitus	27 (60%)
Cardiovascular disease	30 (66.67%)
Anemia	41 (91.11%)
Hypoalbuminemia	22 (48.89%)
Using anti-HTN medicines	16 (35.56%)
Pre-dialysis SBP <100mmHG	37 (82.22%)
Uremia	2 (4.44%)

The incidence of IDH secondary to treatment failure, as well as the incidence of recurrent IDH were significant in patients who had hypoalbuminemia [P=0.03, P=0.01] respectively. Other risk factors that contributed to IDH like presence of anemia, pre-dialysis SBP <100mmHG, and uremia had an impact on SBP and MAP during the hemodialysis session. However, their effects were insignificant (Table 2).

Table 2: Relationship between risk Factors of IDH and Recurrent IDH and Treatment Failure

a: Total number of hemodialysis session

Risk Factor	Recurrent IDH		p-value	Treatment Failure		P-Value
	Yes (n=16)	No (n=29)		Yes (n=28 ^a)	No (n=39 ^a)	
Female gender	8 (50%)	16 (55%)	.74	13 (46%)	20 (51%)	.70
Elderly	10 (63%)	17 (59%)	.80	15 (53.6%)	18 (46.1%)	.83
Diabetes mellitus	10 (63%)	17 (59%)	.80	16 (57%)	20 (51%)	.64
Cardiovascular disease	13 (81%)	17 (59%)	.12	20 (71%)	24 (62%)	.40
Anemia	16 (100%)	25 (86%)	.28	25 (89%)	32 (82%)	.41
Hypoalbuminemia	12 (75%)	10 (35%)	.01	19 (68%)	16 (41%)	.03
Using anti-HTN medicines	4 (25%)	12 (41%)	.27	9 (32%)	13 (33%)	.92
Pre-dialysis SBP <100mmHG	15 (94%)	22 (76%)	.13	25 (89%)	32 (82%)	.41
Uremia	2 (13%)	0 (0%)	.12	2 (7%)	0 (0%)	.17

For the statistical purpose and due to the small number of sample size, midodrine doses were classified into three groups, 19 patients were received 2.5mg to <5mg, 37 patients were received 5mg, and 38 patients were received >5mg of midodrine. For the midodrine frequency, it was classified into two groups. First group included patients who received midodrine for only 3 days per week (n=14), and the second group of patients administered midodrine in daily basic (n=80). The result demonstrated that the incidence of treatment failure and recurrent IDH were statistically significant in patients who received midodrine three time per week in comparison to those who received midodrine for more than three days per week, ((57%, p= 0.02) for the treatment failure and (36%,p=0.04) for the recurrent IDH). (See Figure 1A, 1B). The death event was reported in 23 patients (51.1%), however, the cause of death most likely related to the patient's condition like septic shock (n=9), respiratory distress syndrome (n=1), cardiac arrest (n=2),

septic shock with hypotension (n=9), distress syndrome with cardiac arrest (n=1), and septic shock with heart failure (n=1).

Discussion

IDH is the most frequently adverse event that reported during the hemodialysis procedure. Midodrine seems to be gaining favor as a strategy to aid in management and prevention of IDH. ^(9,10) Midodrine and cool dialysate therapies are the most approaches that have been used.^(16, 17,18,19) It is worth noting the beneficial effects of midodrine in the treatment of IDH and prevention of recurrent IDH with the adjusting the dialysate composition and reducing the ultrafiltration rate continuously throughout the procedure to assist the vascular refilling. Beside to the correction of the modifiable risk factors like an anemia, hypoalbuminemia, and holding the antihypertensive mediations prior to the hemodialysis session. ^(20, 21,22.23,24)

Interestingly, in 2010 the U.S. Food and Drug Administration proposed to withdraw approval of midodrine due to lacking of post marketing studies to predict the clinical outcome of midodrine rather than just improved the hemodynamic parameters. The proposed withdrawal attained disagreement from the American Society of Nephrology, then FDA came to an agreement to remain FDA-approved on the market in the meantime until pharmaceutical company would conduct two clinical trials to verify a clinical benefit of midodrine. ^(25,26) The strength of our study that had a larger sample sizes in comparison to the previous studies were they ranged from 6 to 21 patients. And we gave a rough estimation about the rate of death in among hemodialysis patients who received midodrin. The limitation of our study is that we don't have a comparison group.

Conclusion

Our results suggest that receiving of midodrine is significantly increased the intradialytic blood pressure and decreased the intradialytic hypotensive episodes. A future prospective trial that focus on an important clinical outcomes such as cardiovascular events and mortality with midodrin is warranted.

Abbreviations

IDH: Intradialytic hypotension; SBP: systolic blood pressure; MAP: main arterial pressure; BID: Twice a day; TID: Three times a day.

Declarations

The authors declare that they have no competing interests

Ethics approval and consent to participate:

The study protocol was approved by the King Abdullah International Medical Research Center.

Consent for publication:

Not applicable.

Availability of data and material:

The dataset used for the study is available without patient identifiers from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

SH,ME,MA,YR,& RB conceived and designed the study, supervised the overall execution of the study. SH & MD collected the data, cleaned the database. SH analyzed and interpreted the data. SH & MD wrote the manuscript.

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Figures

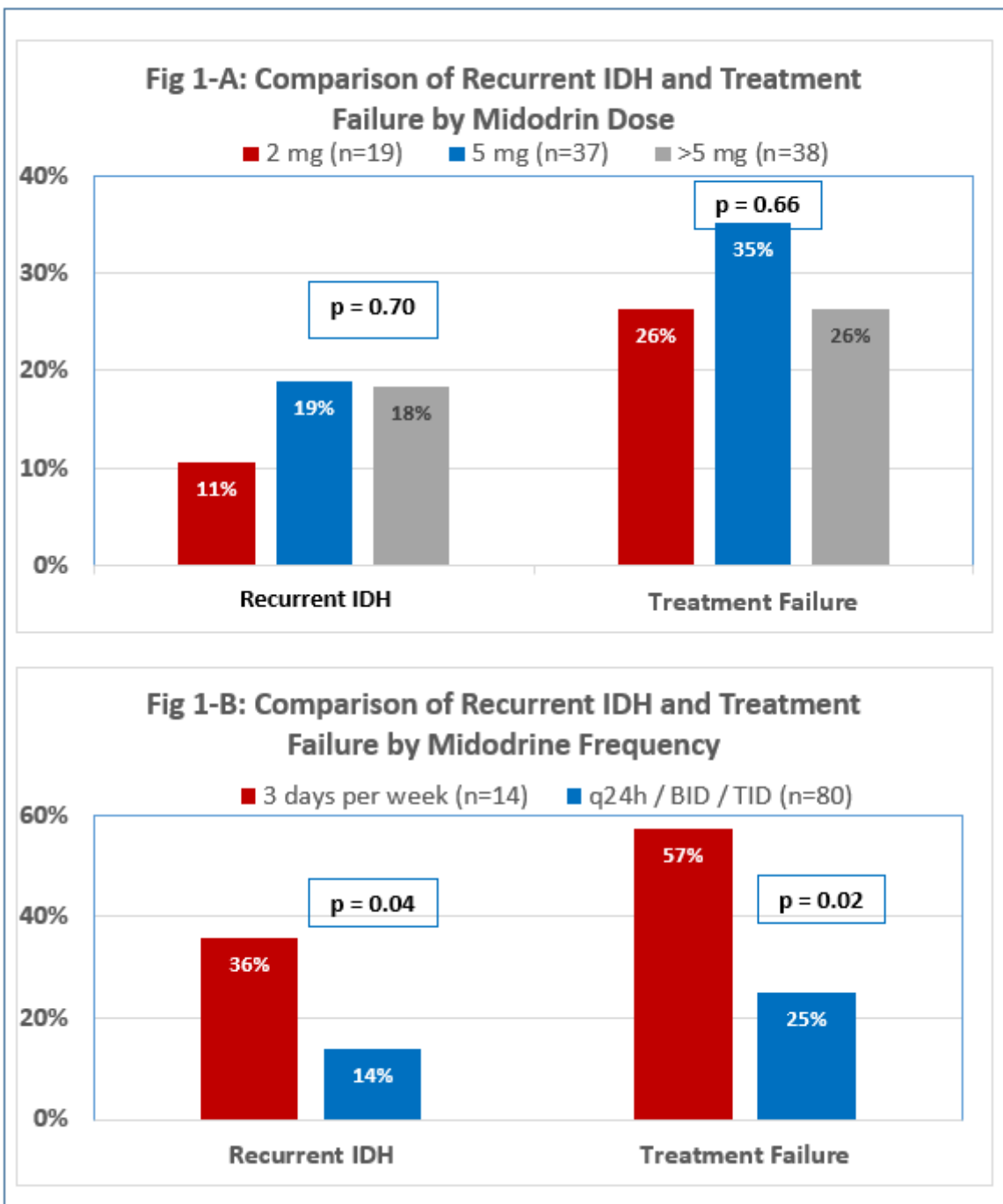


Figure 1

1-A: Comparison of Recurrent IDH and Treatment Failure by Midodrine Dose. 1-B: Comparison of Recurrent IDH and Treatment Failure by Midodrine Frequency; BID: Twice a day; TID: Three times a day.