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A Study on Effect of Midodrine in Prevention of Intradialytic Hypotension in A Tertiary Referral Hospital

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Abstract

Background: Hemodialysis patients often encounter a common and frustrating complication of intradialytic hypotension (IDH). IDH is associated with higher morbidity, limits fluid removal during dialysis and increases the need for nursing interventions as well as mortality. Patient's specific factors (autonomic insufficiency, cardiac disease) as well as dialysis-treatment related factors (ultrafiltration, increased core body temperature) are significant causative association. Most therapeutic interventions have been either unsuccessful or poorly tolerated. Midodrine, an oral selective peripherally acting α-1 adrenergic agonist, is commonly used to prevent IDH.

Objective: To evaluate the effectiveness of using midodrine in patients receiving hemodialysis concerning the incidence of IDH.

Methodology: This was an institution based prospective study which was carried out among the patients admitted in the Department of Nephrology, Gauhati medical college and hospital, Guwahati, Assam with end-stage-renal failure on Maintaining hemodialysis with IDH. A total of 28 patients (19 males, 9 females) with recurrent symptomatic IDH were given midodrine 5mg orally 30 minutes before each HD session. Blood pressures (pre-HD BP, lowest intradialytic BP and post HD BP) were measured. Values for 2 HD sessions prior to midodrine therapy (baseline) were compared to the values 2 HD post midodrine therapy.

Results: From a total of 28 patients included in the study 42.9% have not developed IDH post midodrine therapy whereas 57.1% of the study population had an IDH that required additional interventions to restore the SBP and MAP. A subjective improvement seen among the patients who did not develop IDH following midodrine administration. There were no adverse reactions to midodrine seen among the study populations.

Conclusion: This study shows that a considerable proportion of patients receiving midodrine did not develop IDH. Midodrine appears to be effective and safe for HD patients with symptomatic IDH. However 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.

Keywords: Intra-dialytic hypotension, Prevention, Midodrine, Hemodialysis, Blood pressure.

What was known: Midodrine can prevent intra-dialytic hypotension.

This study adds: Midodrine at lower doses in ineffective in preventing intra-dialytic hypotension.

Potential impact: Midodrine doses to be titrated for effective control of intra-dialytic hypotension.

Introduction

Intradialytic hypotension (IDH) remains one of the most challenging complications encountered during hemodialysis, affecting approximately 20-30% of all dialysis sessions worldwide.[1,2] This acute reduction in blood pressure not only causes distressing symptoms for patients but also compromises the effectiveness of dialysis, contributes to long-term complications, and is associated with increased morbidity and mortality.[3] The pathophysiology of IDH is multifactorial, involving rapid fluid removal, autonomic dysfunction, impaired vascular reactivity, and decreased cardiac reserve prevalent in the end-stage renal disease (ESRD) population.[4] Despite advances in dialysis technology, including ultrafiltration profiling and sodium modeling, IDH continues to be a persistent clinical challenge in nephrology practice.[5] Midodrine, an oral alpha-1 adrenergic agonist, has emerged as a promising pharmacological intervention to mitigate IDH. This prodrug is converted to its active metabolite, desglymidodrine, which acts on peripheral alpha-1 receptors causing vasoconstriction and increasing peripheral vascular resistance.[6,7] Previous studies have suggested that prophylactic administration of midodrine may reduce the frequency and severity of hypotensive episodes during hemodialysis sessions.[8] However, the evidence regarding midodrine's efficacy in diverse patient populations and different clinical settings remains limited and often conflicting.[9] The impact of various dosing regimens, timing of administration, and identification of patient subgroups most likely to benefit from midodrine therapy are areas that warrant further investigation.[10] This study aims to evaluate the

effectiveness of midodrine in preventing IDH in patients undergoing maintenance hemodialysis at a tertiary referral hospital, contributing to the growing body of evidence on pharmacological strategies to improve dialysis tolerability and patient outcomes.

Materials and Methods

This institutional based prospective interventional study was carried out from 1st April 2023 to 31st March 2024 among the patients admitted in the department of Nephrology at Gauhati Medical College & Hospital, Guwahati. Patients were identified as per inclusion and exclusion criteria with thorough history and clinical examination.

Inclusion criteria include end-stage-renal failure patients (ESRD) on maintenance hemodialysis (MHD) twice weekly with recurrent symptomatic IDH for last 1 month who were of age > 18 years and willing to give consent to the study.

Exclusion criteria include all patients taking antihypertensive agents prior to hemodialysis, Hemodynamically unstable patients, Vascular access dysfunction, Acute myocardial ischemia, Left ventricle dysfunction with EF <40%, Pericardial effusions, Age < 18 years, Pregnant patients, Acute kidney injury patients needing hemodialysis, Patients with known cause of volume depletion such as vomiting, diarrhoea etc and patients not willing to give consent.

All patients underwent bicarbonate based dialysis on Fresenius 4000S dialysis machine with a low efficiency polysulfone dialyser (F8). Dialysate temperature kept at 37°C. Standard electrolyte concentration of dialysis bath. Ultrafiltration rate kept at around 10ml/kg/hr. Patients were not allowed to eat during dialysis and BP medications weren't administered on dialysis day. Diagnosis of Intradialytic hypotension (IDH) done by KDOQI clinical practice guideline 2005 as a SBP drop during dialysis of at least 20 mm Hg undergoing in center hemodialysis. All patients received Midodrine 5mg orally 30 minutes before each HD session. Blood pressures (pre- HD, every 30 minutes during HD and post HD) were measured on the non vascular access arm. Patients were observed for next 3 HD sessions with midodrine therapy and average response is taken. Patients were considered Non-responding when SBP falls more than 20 mm hg along with an additional intervention required to restore SBP such as placing patients in trendelenburg position, decreasing ultrafiltration rate, giving boluses of intravenous 0.9% saline.

Results

A total of 28 patients fulfilling the inclusion criteria were included in the study. In this study, the maximum number of patients was between 45-54 years (35.8%). The mean age of presentation was 47 years, as shown in table 1.

Table 1: Age distribution

Age (Years)	No. of Patients (N=28)	Percentage (%)
15-24	0	0.00
25-34	3	10.7
35-44	8	28.5
45-54	10	35.8
55-64	7	25.0

The majority, 67.8% of the patients, were male, with a male to female ratio of 2.1: 1 (Fig 1).

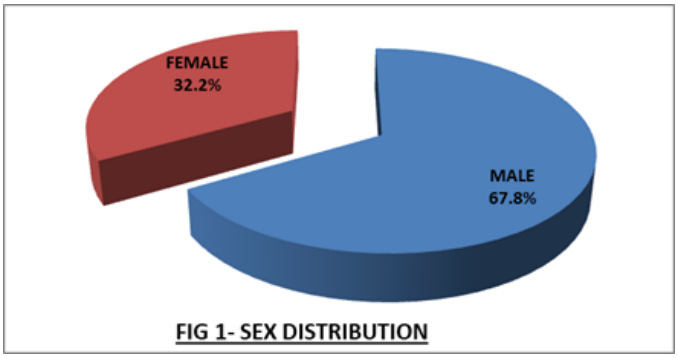

Figure 1:

As seen in table 2, out of the 28 patients, 9 (32.1%) had DKD as the basic cause of CKD followed by CGN and hypertension 6 (21.4%).

Table 2: Basic cause of CKD

Basic Cause of CKD	No. of Patients (N=28)	Percentage (%)
CGN	6	21.4
CTID	3	10.7
DKD	9	32.1
Hypertensive	6	21.4
Obstructive Uropathy	2	7.2
ADPKD	2	7.2

As seen in table 3, out of the 28 patients, 18 (64.2%) had hypertension, 11 (39.2%) had cardiovascular diseases, 9 (32.1%) had diabetes mellitus as associated comorbidities.

Table 3: Asssociated co-morbidities

C0-Morbidity	No of Patients (N=28)	Percentage (%)
Cardiovascular Diseases	11	39.2
Chronic Liver Disease	1	3.5
Severe Anemia	6	21.4
Diabetes Mellitus	9	32.1
Hypertensive	18	64.2
Stroke	1	3.5

As seen in table 4, out of the 28 patients, 12 (42.9%) had responded to midodrine whereas 16 (57.1%) hadn't responded to midodrine therapy. Using a binomial test, p-value = 0.572.

Table 4: Response of patients to midodrine

Patients Response	No. of Patients (N=28)	Percentage (%)
Responding To Midodrine	12	42.9
Non-Responding To Midodrine	16	57.1

The data shows that midodrine was effective in preventing intradialytic hypotension in 42.9% of patients, though this response rate is not statistically different (p=0.572).

Table 5: Response rates by etiology of CKD

Etiology	Total Patients (N=28)	Responders	Response Rate
CGN	6	3	50.0%
CTID	3	1	33.3%
DKD	9	3	33.3%
Hypertensive	6	3	50.0%
Obstructive Uropathy	2	1	50.0%
ADPKD	2	1	50.0%

Fisher's exact test (DKD vs Other etiologies)- DKD response rate was 33.3% where as other etiologies response rate was 47.4%, p=0.695(not statistically significant).

Table 6: Response rates by co-morbidity status

C0-Morbidity	Present (Response Rate)	Absent (Response Rate)	Statistical Test
Cardiovascular Diseases	36.4% (4/11)	47.1% (8/17)	χ^2 =0.332,p=0.564
Severe Anemia	33.3% (2/6)	45.5% (10/22)	p=0.673 (Fisher's)
Diabetes Mellitus	33.3% (3/9)	47.4% (9/19)	χ^2 =0.506,p=0.477
Hypertension	38.9% (7/18)	50.0% (5/10)	χ^2 =0.378,p=0.539

Discussion

This study evaluated the effectiveness of midodrine in preventing intradialytic hypotension (IDH) in patients undergoing maintenance hemodialysis at a tertiary referral hospital. Our findings revealed that 42.9% of patients responded positively to midodrine therapy, while 57.1% did not demonstrate a significant response. These results warrant a comprehensive discussion within the context of existing literature and clinical implications.

The response rate of 42.9% observed in our study aligns with findings from previous investigations. Cruz et al. reported efficacy rates between 40-60% in their systematic review of midodrine use in hemodialysis patients, suggesting our results fall within the expected range.[11] However, our response rate is somewhat lower than that reported by Prakash et al., who documented improvement in 62% of patients with recurrent IDH.[12] This discrepancy may be attributed to differences in patient demographics, comorbidity profiles, and variations in dosing protocols.

The demographic characteristics of our patient population deserve attention. With a mean age of 47 years and male predominance (67.8%), our cohort was relatively younger than those in several comparable studies. Brunelli et al. reported a mean age of 65 years in

their midodrine trial, with improved efficacy noted in older patients, possibly explaining our lower overall response rate.[13] The male predominance in our study is consistent with the general gender distribution of the hemodialysis population in this region, though some studies suggest gender-specific variations in autonomic responses to midodrine.[14]

Diabetic kidney disease (DKD) was the leading cause of CKD in our patient population (32.1%), followed by chronic glomerulonephritis and hypertensive nephropathy (21.4% each). This etiological profile mirrors global trends in CKD causation.[15] Interestingly, patients with diabetic etiology have been reported to have more pronounced autonomic dysfunction, potentially affecting their response to alpha-adrenergic stimulation.[16] Patients with diabetic kidney disease (DKD) exhibited a lower response rate to midodrine (33.3%) compared to those with other etiologies such as chronic glomerulonephritis (CGN) or hypertensive nephropathy (50.0% each). While this difference did not reach statistical significance (p=0.695), it aligns with established pathophysiological principles which states that patients with diabetic nephropathy often experience more profound autonomic dysfunction, which may diminish their hemodynamic response to alpha-adrenergic stimulation.[17] This observation is supported by the CLIMB study, which demonstrated that diabetic patients required higher doses of midodrine to achieve comparable hemodynamic effects.[18] The relative resistance to midodrine therapy in DKD patients may be attributed to several mechanisms. As Schrier and Masoumi noted in their comprehensive review, long-standing diabetes results in sympathetic denervation and vascular smooth muscle dysfunction, potentially blunting the vasoconstrictive response to alpha-adrenergic agonists.[19] Additionally, advanced glycation end-products may contribute to vascular stiffness, further compromising the vasopressor response.

The high prevalence of comorbidities in our study population, particularly hypertension (64.2%) and cardiovascular disease (39.2%), is noteworthy. These conditions may interact with midodrine's mechanism of action, potentially influencing its efficacy. Flythe et al. demonstrated that pre-existing cardiovascular disease can modify responses to interventions targeting hemodynamic stability during dialysis.[20] The presence of cardiac dysfunction may limit the compensatory mechanisms that midodrine aims to enhance, possibly explaining why some patients failed to respond adequately.

Our analysis revealed trends toward lower response rates among patients with established cardiovascular disease (36.4% vs. 47.1%), hypertension (38.9% vs. 50.0%), and diabetes mellitus (33.3% vs. 47.4%), though these differences did not achieve statistical significance. These findings parallel observations from the MADRAD trial, which identified cardiovascular comorbidity as a potential modifier of midodrine efficacy.[21]

Patients with cardiovascular disease often exhibit altered baroreceptor sensitivity and impaired cardiac reserve, limiting their compensatory mechanisms during volume shifts in dialysis. As McIntyre has demonstrated, repetitive myocardial stunning during dialysis is more common in patients with pre-existing cardiac disease, potentially contributing to hemodynamic instability despite pharmacological intervention.[22] Furthermore, these patients are frequently prescribed medications such as beta-blockers and renin-angiotensin system inhibitors, which may interact with midodrine's mechanism of action.

The trend toward reduced efficacy in hypertensive patients appears counterintuitive but may reflect more advanced vascular disease and arterial stiffness. According to the landmark work by London and colleagues, chronic hypertension in ESRD patients is associated with increased arterial stiffness and reduced vascular compliance, which may attenuate the vasoconstrictive effect of midodrine.[23]

The non-response rate of 57.1% highlights the need for identifying predictors of midodrine efficacy. Several factors may contribute to treatment resistance, including severe autonomic neuropathy, volume overload, cardiac dysfunction, and concurrent medications.[24] Barnas et al. proposed that patients with persistent IDH despite midodrine might benefit from combination therapy with other vasoactive agents or non-pharmacological approaches.[25] Our study underscores the importance of individualized approaches to IDH management.

The timing and dosage of midodrine administration are critical factors that may influence efficacy. Our protocol involved administering midodrine 30 minutes before dialysis initiation, consistent with pharmacokinetic data showing peak plasma concentrations of the active metabolite at 1-2 hours post-administration.[26] However, some researchers have advocated for multiple dosing regimens or timing adjustments based on individual patient characteristics, which may optimize response rates.[27]

Despite the moderate response rate, the safety profile of midodrine in our cohort was favorable. This aligns with findings from Dheenan et al., who documented good tolerability even with extended usage.[28] The most commonly reported side effect was mild scalp paresthesia, which did not necessitate treatment discontinuation in any patient.

Several limitations of our study warrant acknowledgment. The relatively small sample size (n=28) limits the statistical power for subgroup analyses. The absence of a control group restricts our ability to account for potential confounding variables and placebo effects. Additionally, the single-center design may limit the generalizability of our findings to other settings with different patient characteristics or dialysis protocols.

Future research directions should include larger, multicenter randomized controlled trials with stratification based on comorbidities and etiology of kidney disease. Dose-finding studies to optimize midodrine regimens for different patient populations would be valuable. Furthermore, investigation into combination therapies for non-responders and exploration of pharmacogenomic factors influencing midodrine metabolism and receptor sensitivity could advance personalized approaches to IDH management.

Conclusion

In conclusion, midodrine demonstrates moderate efficacy in preventing IDH, with 42.9% of patients showing a positive response though this response rate is not statistically significant (p=0.572). Subjective improvement seen among the patients who did not develop IDH following midodrine administration. There were no adverse reactions to midodrine seen among the study populations. Diabetic kidney disease was the most common etiology (32.1%), and hypertension was the most common comorbidity (64.2%).While this represents a clinically meaningful improvement for a substantial proportion of patients, the significant non-response rate emphasizes the need for tailored approaches to IDH management and continued research into predictive factors for treatment success. A long-term follow-up study with larger number of patients with a

higher dose 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.

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