

Intradialytic Hypotension in Hemodialysis Patients and Its Relation to Duration of Hemodialysis

Short title: Intradialytic Hypotension in End-Stage Renal Disease.

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Abstract:

Background and Aim: Intradialytic hypotension (IDH) is known to be one of the most frequent complications of hemodialysis. This study aims to assess IDH frequency in chronic kidney disease (CKD) patients on chronic hemodialysis.

Patients and Methods: A cross-sectional study was conducted on hemodialyzed end-stage kidney disease patients (ESRD, 94 patients) on regular hemodialysis. All patients were treated with high-permeability membranes. We excluded patients with advanced heart failure according to the criteria of the European Society of Cardiology and clinically unstable patients who required hospital admission. So, our study included 90 patients after the exclusion of 4 patients due to advanced heart failure and patients needing hospital admission. For all patients, a full history was taken before the dialysis session. Blood pressure (BP) was measured with a mercury sphygmomanometer before, after, and every 60 min during the hemodialysis session (a total of 5 measurements) for 10 consecutive dialysis sessions.

Results: Only 25 patients (27.8 %) had IDH. Patients suffering from IDH had a longer duration of dialysis in comparison to those patients without IDH (6.84 ± 1.17 vs. 3.75 ± 1.13 (years)), with lower serum albumin (3.5 ± 0.15 vs. 4.21 ± 0.12 (g/dl)) and significantly higher glycosylated haemoglobin (8.09 ± 2.22 vs. 5.45 ± 1.90 (%)). Patients suffering from autonomic neuropathy were more liable to IDH based on heart rate response to deep breathing test (76% vs. 27.75%) and based on blood pressure response to standing (68% vs. 23.1%) in comparison to those without IDH.

Conclusion: Based on the current study, predictors of IDH were female sex, long duration of dialysis, low serum albumin, high glycosylated haemoglobin, and autonomic neuropathy based on heart rate response test and BP response test.

Keywords: Blood pressure, heart rate, autonomic neuropathy.

Introduction:

Intradialytic hypotension (IDH) is known to be one of the most common complications of haemodialysis (1). Intradialytic hypotension is defined as a reduction in systolic BP by ≥ 20 mm Hg or a decrease in mean arterial pressure of 10 mm

Hg complicated by manifestations such as muscle cramps, central signs such as dizziness and headache, or gastrointestinal signs such as nausea and vomiting according to The National Kidney Foundation (2).

IDH increases the risk of morbidity and mortality (3). IDH is mainly due to rapid blood volume reduction by ultrafiltration and insufficient body compensatory mechanisms

like left ventricular dysfunction, inadequate plasma refilling, and decreased vasoconstriction caused by autonomic nervous system dysfunction (4).

Diabetes is the most common cause of chronic kidney failure (2). Diabetic patients are at a higher risk of cardiovascular diseases than non-diabetics. Autonomic neuropathy is a common complication of diabetes and is associated with IDH (5). In this study, we want to assess the frequency of IDH among ESRD patients on regular hemodialysis and its predictors.

Patients and Methods

This work was conducted after obtaining approval by the Medical Ethics Committee of the Faculty of Medicine at Assiut University with IRB number (17100709). Also, written informed consent was obtained from all participants before being enrolled in the study. The study was registered on Clinicaltrials.gov Identifier: NCT03870594.

A cross-sectional study was carried out on all hemodialyzed patients of the hemodialysis unit in Assiut Health Insurance Hospital from July 2021 to December 2021. All patients received 3 hemodialysis sessions per week. The blood flow was from 200 to 300 mL/min. All patients were treated with high-permeability membranes.

Selection Criteria

During the study period, a total of 94 patients were eligible for enrollment in the study. Out of those patients, four patients were excluded due to advanced heart failure (three patients) and clinical instability requiring hospital admission (one patient).

Methods

Before the beginning of the dialysis session, a full history was taken, including age, presence of diabetes and its duration, and duration of hemodialysis, and a clinical examination was performed on each patient. Before each session, interdialytic weight gain was measured. Before and after every 1 hour during the hemodialysis session, blood pressure (BP) was measured with a mercury sphygmomanometer (5 measurements) for 10 consecutive dialysis sessions.

Intradialytic hypotension (IDH) was defined as a reduction in systolic BP by ≥ 20 mm Hg or a decrease in mean arterial pressure of 10 mm Hg complicated by symptoms. Autonomic neuropathy (AN) was measured in all patients by 2 cardiovascular tests:

1. Blood pressure response to standing: Blood pressure was measured when the patient was supine and 2 minutes after standing. The difference in BP in both positions was recorded.

Normally: ≤ 11 , AN+: ≥ 30 .

2. Changes in heart rate after deep breathing: ECG was recorded when the patient was supine, then when the patient did 6 maximum breaths per minute.

E: I ratio was measured: (6).

E: I ratio

$$= \frac{\text{Mean value of longest RR interval during expiration}}{\text{Mean value of shortest RR interval during deep inspiration}}$$

Normal: ≥ 1.21 , AN+: ≤ 1.10 .

Serum urea, creatinine, serum electrolytes, complete blood count, serum protein, albumin, liver function tests, glycosylated hemoglobin, and fasting blood glucose were measured by blood samples.

Statistical Analysis

Data was collected and analyzed using SPSS (Statistical Package for the Social Sciences, version 20, IBM, Armonk, New York). Quantitative data were expressed as mean \pm standard deviation (SD). Student's t-test compared quantitative data with a normal distribution. Nominal data are given as numbers (n) and percentages (%). Predictors of IDH were determined by logistic regression analysis, while the '[=]' receiver operator characteristics curve was used to assess the accuracy of different predictors in predicting IDH. The confidence level was kept at 95%; hence, the P value was considered significant if < 0.05 .

Results

A total of 90 patients with ESRD who were on regular HD were registered in this study. Out of those patients, 25 (27.8%) patients had Intradialytic hypotension (IDH), while the other 65 (72.2%) patients didn't suffer from IDH (Figure 1).

Baseline data of studied patients based on the development of IDH (Table 1):

Patients of the IDH group had an insignificantly higher mean age (59.24 ± 6.86 vs. 53 ± 12.46 (years); $p < 0.13$), while the longer duration of dialysis was significant (6.84 ± 1.17 vs. 3.75 ± 1.13 (years); $p < 0.001$). The majority (76%) of patients with IDH were females, while the majority (53.8%) of patients without IDH were males, with significant differences between both groups ($p = 0.04$).

Pre-dialytic hemodynamics of studied patients based on the development of IDH (Table 2):

It was found that both groups of patients, based on the development of IDH had insignificant differences regarding pre-dialytic hemodynamics and laboratory data, except for significantly lower serum albumin (3.21 ± 0.28 vs. 3.89 ± 0.33 (g/dl); $p < 0.001$), and significantly higher glycosylated haemoglobin (8.09 ± 2.22 vs. 5.45 ± 1.90 (%); $p < 0.001$) among patients with IDH.

Frequency of autonomic neuropathy (AN) in the patients based on IDH (Table 3):

Patients with IDH had a significantly higher frequency of AN based on changes in heart rate after deep breathing test (76% vs. 27.75%; $p < 0.001$) and based on blood pressure response to standing (68% vs. 23.1%; $p < 0.001$) in comparison to those without IDH.

Predictors of intradialytic hypotension among the studied patients (Table 4):

In this study, predictors of IDH were: female sex (odd's ratio (OR= 1.56), duration of dialysis (OR=1.11), serum albumin (OR= 2.89), glycosylated haemoglobin (OR= 2.11), AN based on HR response test (OR= 4.33), and AN based on BP response test (OR= 3.90).

Accuracy of autonomic neuropathy in the prediction of IDH (Table 5, Figure 2):

AN based-on HR response test had 74.5% accuracy with the area under the curve of 0.74 for prediction, while AN based-on BP response test had 73.8% accuracy with the area under the curve of 0.72.

Legend of Tables**Table (1):** Baseline data of studied patients based on the development of IDH

	Development of IDH		P value
	Yes (n= 25)	No (n=65)	
Age (years)	59.24 ± 6.86	53 ± 12.46	0.13
Sex			0.04
Male	6 (24%)	30 (46.2%)	
Female	19 (76%)	35 (53.8%)	
Residence			0.14
Rural	14 (56%)	46 (70.8%)	
Urban	11 (44%)	19 (29.2%)	
BMI (kg/m ²)	24.80 ± 2.14	23.91 ± 2.78	0.15
Duration of dialysis (years)	6.84 ± 1.17	3.75 ± 1.13	< 0.001

Data expressed as frequency (percentage), mean \pm SD. *P*-value was significant if < 0.05 . **IDH:** intradialytic hypotension; **BMI:** body mass index.

Table 2: Pre-dialytic hemodynamics and laboratory data of studied patients based on the development of intradialytic hypotension

	Development of IDH		P value
	Yes (n= 25)	No (n=65)	
Systolic blood pressure (mmHg)	117.48 ± 8.50	120.20 ± 7.36	0.13
Diastolic blood pressure (mmHg)	85.04 ± 10.43	83.43 ± 9.95	0.50
Heart rate (b/minute)	76.92 ± 3.21	78.40 ± 5.41	0.20
Respiratory rate (c/minute)	23.11 ± 2.06	23.76 ± 2.82	0.21
Hemoglobin (g/dl)	8.63 ± 1.52	8.99 ± 2.04	0.13
Platelets (10 ³ /ul)	262.20 ± 113.45	270.19 ± 155.65	0.50
Leucocytes (10 ³ /ul)	8.91 ± 3.12	8.41 ± 2.94	0.20
Urea (mg/dl)	25.26 ± 11.75	24.01 ± 10.75	0.42
Creatinine (mg/dl)	5.32 ± 2.55	5.89 ± 2.79	0.85
Aspartate transaminase (u/l)	23.64 ± 22.54	25.87 ± 20.28	0.47
Alanine transaminase (u/l)	17.44 ± 6.12	22.03 ± 13.19	0.63
Protein (g/dl)	7.13 ± 0.7	7.3 ± 0.95	0.38
Albumin (g/dl)	3.5 ± 0.15	4.21 ± 0.12	< 0.001
Bilirubin (mmol/l)	4.46 ± 2.84	3.54 ± 2.44	0.65
Direct bilirubin (mmol/l)	1.62 ± 1.52	1.18 ± 1.09	0.09
Prothrombin time (s)	13.30 ± 1.38	12.75 ± 1.65	0.12
Prothrombin concentration (%)	75.20 ± 13.15	78.78 ± 14.79	0.13
INR	1.15 ± 0.13	1.12 ± 0.20	0.13
Glycosylated haemoglobin (%)	8.09 ± 2.22	5.45 ± 1.90	< 0.001
Calcium (mg/dl)	9.6 ± 0.9	9.5 ± 0.9	0.49
Phosphorus (mg/dl)	5.11 ± 2.11	5.01 ± 2.22	0.90
Sodium (mmol/l)	134.98 ± 6.98	133.11 ± 4.67	0.11
Potassium (mg/dl)	4.06 ± 1.11	3.99 ± 0.56	0.19

Data expressed as mean ±SD. *P*-value was significant if < 0.05. **IDH:** intradialytic hypotension; **INR:** international randomized ratio

Table 3: Frequency of autonomic neuropathy in the patients based on IDH

Frequency of AN	Development of IDH		P value
	Yes (n= 25)	No (n=65)	
HR response to deep breathing			< 0.001
AN	19 (76%)	18 (27.7%)	
No-AN	6 (24%)	47 (72.3%)	
BP response to standing			< 0.001
AN	17 (68%)	15 (23.1%)	
No-AN	8 (32%)	50 (76.9%)	

Data expressed as frequency (percentage). *P*-value was significant if < 0.05. **IDH:** intradialytic hypotension; **AN:** autonomic neuropathy; **HR:** heart rate; **BP:** blood pressure.

Table 4: Predictors of intradialytic hypotension among the studied patients

Variables	Odd's ratio	95% CI	P value
Female	1.56	1.40-3.11	0.03
Age (years)	1.01	0.34-2.11	0.18
Duration of dialysis (years)	1.11	1.02-2.19	0.02
Serum albumin (mg/dl)	2.89	2.10-6.01	< 0.001
HbA1c (%)	2.11	1.56-3.99	0.02
AN based-on HR response test	4.33	2.80-10.44	< 0.001
AN based-on BP response test	3.90	2.50-5.55	< 0.001

CI: confidence interval; **HbA1c:** glycosylated haemoglobin; **AN:** autonomic neuropathy; **HR:** heart rate; **BP:** blood pressure.

Table 5: Accuracy of autonomic neuropathy in the prediction of IDH

	AN based-on HR response test	AN based-on BP response test
Sensitivity	76%	68%
Specificity	73%	77%
Positive predictive value	52%	53.2%
Negative predictive value	88.7%	86.2%
Accuracy	74.5%	73.8%
Area under curve	0.74	0.72
P value	< 0.001	< 0.001

CI: confidence interval; **HbA1c:** glycosylated haemoglobin; **AN:** autonomic neuropathy; **HR:** heart rate; **BP:** blood pressure.

Legend of Figures

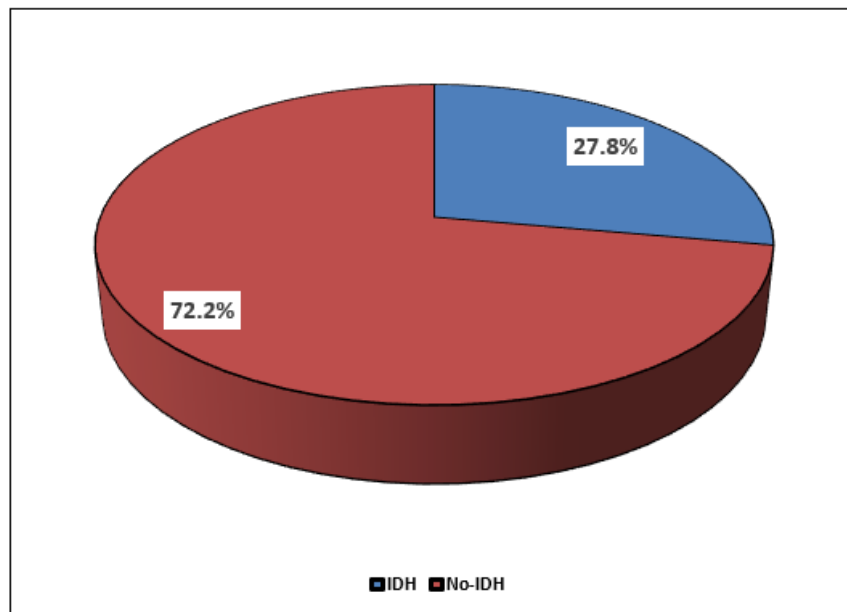


Figure 1: Frequency of IDH in the studied patients. IDH: intradialytic hypotension

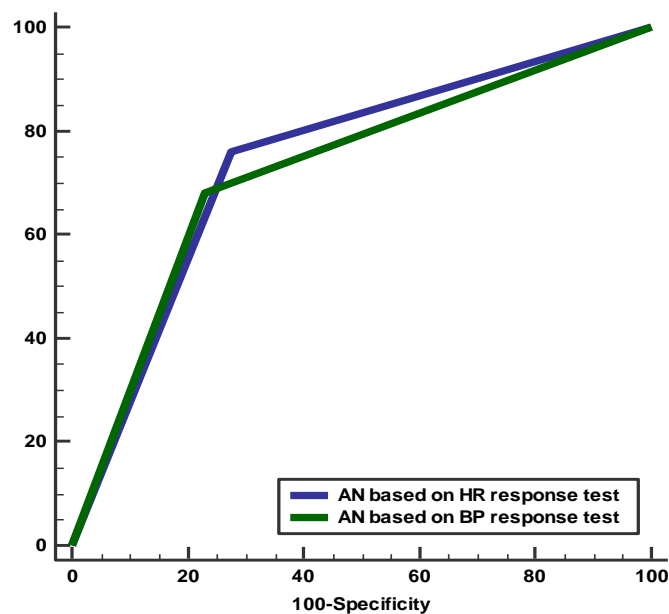


Figure 2: Accuracy of autonomic neuropathy in the prediction of IDH intradialytic hypotension

Discussion

We conducted this work to assess the frequency of IDH and related risk factors. Ninety patients with ESRD were on regular HD and enrolled in the study. Of those patients, 25 (27.8%) had IDH, while the other 65 (72.2%) didn't suffer from IDH.

The incidence of IDH is different in many studies due to many IDH definitions and patient factors such as age, presence of diabetes and cardiac diseases, and interdialytic weight gain, so IDH has a discrepant prevalence. (7, 10, 11)

This study found that patients of the IDH group had an insignificantly higher mean age (59.24 ± 6.86 vs. 53 ± 12.46 (years); $p = 0.13$) than those without IDH. In agreement with the current study, **Park et al.** stated that both groups had insignificant differences as regards the age of patients (53.2 ± 12.7 vs. 57.3 ± 13.3 (years); $p = 0.20$). (12) This was also consistent with other studies. (7, 10, 11)

In contrast, **Capuano et al.** stated that the incidence of IDH is higher in older patients than in younger patients, which could be attributed to relatively younger patients in their study. (13)

Another finding in this study was that patients with IDH had a longer duration of dialysis (6.84 ± 1.17 vs. 3.75 ± 1.13 (years); $p < 0.001$). This was agreed with the study of **Keane et al.**, who stated that a longer duration of dialysis for patients with IDH is needed (14). However, the study of **AL-Etreby et al.** showed that both groups had insignificant differences as regards duration of dialysis (5.8 ± 0.89 vs. 4.37 ± 0.68 (years); $p = 0.25$). This inconsistency may be related to the difference in the studied population, sample size, and selection bias. (15)

Here, in this study, the majority (76%) of patients with IDH were females, while the majority (53.8%) of patients without IDH were males, with significant differences between both groups ($p = 0.04$). This finding agreed with **Keane et al.**, who reported female predominance among patients with IDH (47% vs. 41%) (14). And yet other

studies reported no sex predominance among patients with IDH. (10, 12, 15)

We found that blood pressure, heart rate, and respiratory rate before dialysis did not affect the frequency of IDH. These results agreed with previous studies that revealed no significant differences between IDH and non-IDH groups regarding pre-dialysis blood pressure and heart rate (12). In contrast, earlier studies said that predialytic blood pressure could predict changes in systolic blood pressure during hemodialysis. The higher the SBP, the lower the blood pressure during hemodialysis, increasing the risk of IDH. (15, 16)

The baseline laboratory data showed no significant differences between the two studied groups (either with IDH or without IDH) except for significantly lower serum albumin (3.5 ± 0.15 vs. 4.21 ± 0.12 (g/dl); $p < 0.001$) and significantly higher glycosylated haemoglobin (8.09 ± 2.22 vs. 5.45 ± 1.90 (%); $p < 0.001$) among patients with IDH.

Nakamoto et al. agreed with this study on the effect of hypoalbuminemia on the occurrence of IHD. (18)

In this study, it was found that patients with IDH had a significantly higher frequency of AN based on changes in heart rate in response to deep breathing tests (76% vs. 27.75; $p < 0.001$) and based on blood pressure response to standing (68% vs. 23.1%; $p < 0.001$) in comparison to those without IDH. This result is consistent with **Sato et al.**, who found that the presence of autonomic neuropathy (including diabetic neuropathy) is a risk factor for IDH. (19)

Autonomic dysfunction has been considered to be an essential factor in the occurrence of intradialytic hypotension. **Rubinger et al.** agreed with this study in that low heart rate response tests increase the risk of intradialytic hypotension in chronic hemodialysis patients (20). Low heart rate response increases the risk of perioperative hypotension in many surgeries. (21)

Based on the current study, predictors of IDH were; female sex (odd's ratio (OR)= 1.56), duration of dialysis (OR=1.11), serum albumin (OR= 2.89), glycosylated haemoglobin (OR= 2.11), AN based-on HR response test (OR= 4.33) and AN based-on BP response test (OR= 3.90). It was found that the AN based on the HR response test had 74.5% accuracy, with the area under the curve being 0.74 for the prediction of IDH, while the AN based on the BP response test had 73.8% accuracy, with the area under the curve being 0.72.

The main limitations of the current study included a relatively small sample size, being conducted in a single center, and a prolonged duration of follow-up for those patients to assess the long-term effect of IDH on such patients.

Conclusion

IDH was reported in 27.8% of patients with ESRD in the current study. Predictors for such complications were female sex, long duration of dialysis, low serum albumin, high glycosylated haemoglobin, and autonomic neuropathy based on heart rate response test and BP response test. Future studies are warranted to confirm such findings.

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