Original Research Article

Inotropic Support in Severe Intra-dialytic Hypotension: A Comparison of Predialysis, and Intradialytic Dopamine. A Single Center Retrospective Study.

Abstract

Introduction

Despite advances made in dialysis delivery, management strategies for intradialytic hypotension (IDH) has largely remained suboptimal hence the need for more interventions to improve on it.

Methods

We compared in this retrospective study, predialysis dopamine (PDD) with intra-dialytic dopamine (IDD) in the treatment of severe IDH.

Results

Of the 2968 sessions, 518 (17.45%) had symptomatic IDH, of this, 9.65% had PDD while 12.16% had IDD. The mean age of all participants, with PDD, and with IDD were 50.73 ± 6.51 years, 64.48 ± 8.22 years and 64.64 ± 10.31 years respectively, P=0.001. The intra-dialytic pulse rate increases, with BP reductions, were more with IDD treatments than PDD. Dialysis BFR, ultrafiltration volume, duration and dose were higher with PDD treatment, P=0.002, P=0.03, P=0.04 and P<0.001 respectively.

Hospitalization, dialysis termination and intra-dialytic death were commoner with IDD treatment, P=0.08, P=0.001 and P=0.002. PDD was commoner in females, advancing age and diabetes, P=0.08, P=0.93 and P=0.06. Independent associates of IDD were lower predialysis systolic, and diastolic BP, shorter dialysis duration, dialysis termination and intra-dialytic death.

Conclusion:

The prevalence of overall IDH, of severe IDH using a nadir systolic BP less than 90 mmHg was 17.45%, of severe IDH using a nadir systolic BP less than 90 mmHg was 12.28%, and of severe IDH using a minimum 20 mmHg fall in systolic BP were 17.65%. Low dose PDD treatment of IDH allows for a relative optimization of the prescribed dialysis, gives higher dialysis dose and reduces the frequencies of dialysis termination and intradialytic death.

Keywords

Maintenance hemodialysis, Pre-dialysis dopamine, intra-dialytic dopamine, tachycardia, dialysis dose, dialysis termination, intra-dialytic death.

Introduction

Despite advances made over the years in managing intra-dialytic hypotension (IDH), its prevalence has remained high and likewise its complications [1]. This has largely be due to the complex interactive forces associated with its occurrence (patient, disease or dialysis related factors), from suboptimal preventive and treatment strategies, or from conditions that limit effective response to management strategies [2]. The occurrence of IDH is strongly tied to dialysis ultrafiltration, on a background of ineffective compensatory response to fluid removal [1-3]. Ultrafiltration can be minimized to reduce the frequency of IDH, however, this has to be weighed against the consequences of fluid overload which limits patients' quality of life (QOL), precipitating heart failure and other conditions associated with increased mortality [2, 4].

The relationship between the inter-dialytic weight gain (IDWG) and the ultrafiltration rate (UFR) for any session is dependent on the interplay of forces such as the blood pressure (BP), blood flow rate (BFR) and the cardiovascular status particularly the cardiac reserve [5, 6]. Various comorbidities like hypertension, diabetes, dyslipidemia and peripheral vascular disease (PVD) are known to be associated with CKD, more so with end stage renal disease (ESRD) and these

worsen the clinical outcome of the disease [7]. CKD is particularly known to be associated with worsening cardiovascular profile with more cardiac events and death [8, 9]. Commonly, these comorbidities increases the risk of intra-dialysis complications and poor treatment outcome resulting in lower dialysis doses, higher frequencies of hospital admission, poor QOL and mortality [10, 11]. An adequate dialysis dose usually entails higher BFR and UFR but these are expectedly, associated with BP reduction which might be severe enough to precipitate IDH and tissues ischemia that could lead to myocardial ischemia, stunning and infarction, and brain damage [12]. The institution of measures to prevent wide BP reduction while maintaining relatively higher UFR would therefore be needed to deliver adequate dialysis doses, prevent IDH and its complications thereby decreasing morbidity and mortality [13].

Most often, routine measure at treating IDH (removing/treating precipitants, fluid resuscitation, amongst others) are not enough, particularly in low income nations (LINs) due to the non-availability/application of modern strategies used to manage IDH [14].

Various strategies involving the relaxation of the left ventricle left ventricular hypertrophy (LVH) and reducing tachycardia have be employed in managing IDH with minimal success [15, 16]. Inotropes such as midodrine, dobutamine, sertraline and droxidopa, and others including antidiuretic hormone analogs and adenosine A1 receptor antagonist have been used in the past to prevent and treat severe or persistent IDH with varying success rates [17-22]. Wen-Yuan et al reported intra-dialytic use of dopamine with improvement in the dialysis dose, reductions in the frequencies of IDH, dialysis termination, hospital admissions, and no worsening of patients' QOL [23]. The occurrence of IDH prior to inotropic support could lead to further worsening of kidney function [3, 13]. Dopamine and other inotropes have been used to maintain effective blood pressure and tissue perfusion prior to, during and after major maneuvers on medical,

surgical and intensive care units (ICUs) [24]. Considering the benefits associated with the avoidance of IDH, measures to avoid its occurrence are worth undertaking. The use of inotropes in managing IDH is not well reported worldwide, more so, it has not been reported from a LIN. We hypothesize that pre-dialysis dopamine (PDD) is more effective in preventing and treating IDH compared to intra-dialytic dopamine (IDD). We compare the pre-dialysis and intra-dialytic use of dopamine in preventing and treating severe IDH in a low income setting.

Materials and Methods

A retrospective cohort study of 2968 maintenance hemodialysis (MHD) sessions received by 557 participants, and of which dopamine was used in managing 36 participants who had IDH in 113 sessions. Participants were aged between 16 and 81 years and had CKD using the KDOQI 2012 diagnostic criteria [25]. The studied sessions were given from August 2018 to July 2021 at the dialysis suite of Babcock University Teaching Hospital, Ilishan-Remo, Nigeria. The sessions were grouped into 2 cohorts, with PDD, and with IDD.

Variables retrieved from participants' case notes and dialysis chats included: age, gender, etiology, and type of kidney disease, hospitalizations, comorbidities, oxygen saturation (SPO_2), pulse rate (PR) and blood pressure (BP), time, and dose of dopamine administered. The results of serum electrolytes urea and creatinine, and the monthly calculated urea reduction ratio (URR) and Kt/V were recorded.

According to the dialysis unit's protocol:

Indication for predialysis dopamine: 3 or more consecutive episodes of severe IDH (intradialytic systolic BP less than 90mmHg with symptoms (nausea, yawning, cramps, dizzy spells, syncope, body pains and/or chest discomfort in which nursing intervention was

unsuccessful leading to dialysis termination, after ruling out and/or correcting modifiable factors such as fever, drug effect or food intake).

Indication for intradialytic dopamine: 3 or more consecutive episodes of severe IDH (at least 20 mmHg drop in systolic BP to less than 100 mmHg, with symptoms and, in which nursing interventions were unsuccessful leading to dialysis termination, after ruling out and/or correcting modifiable factors causing IDH).

3. Predialysis dopamine was commenced 30 minutes before dialysis at 2-5ug/kg/min at 10-15 drops/minute (depending on the extent of BP drop) in 200mls of 0.9% saline.

4. Intradialytic dopamine was commenced 2-5ug/kg/min at 10-15 drops/minute (depending on the extent of BP drop) in 200 ml of 0.9% saline.

Exclusion criteria

Sessions in which other inotropes were used were excluded.

Anticoagulation was with unfractionated heparin (5000 IU). All sessions were with a dialysate flow rate (DFR) of 500ml/min. The dialysate sodium, potassium calcium and bicarbonate were 140 mmol/L, 2.0 mmol/L, 2.0 mmol/L and 34 mmol/L respectively. Whenever sodium profiling was carried out prior to dopamine infusion (no sodium profiling was done after commencement of dopamine), the mean dialysate sodium concentration was documented.

The study was approved by the Babcock University Human Research Ethics (BUHREC/723/19, NHREC/24/01/2018).

Definitions

Tachycardia, classified as mild (PR-101-119/min), moderate (PR-120-139/min), severe (PR-140-149/min) and life threatening (PR equals or greater than 150/min) [26].

Hypoxemia, defined as SPO_2 less than 95% [27].

Dopamine doses, classified as low (less than 5ug/kg/min), medium (5.01-9.99ug/kg/min), high (10ug/kg/min or more) [24].

Targeted post dialysis weight (TPDW) defined as predialysis weight plus volume of administered fluid minus UFV [5].

IDH defined as intra-dialytic fall in SBP of 20 mmHg or more [3].

Severe IDH defined as 3 or more consecutive episodes of intradialytic systolic BP less than 90mmHg with symptoms, in which nursing intervention was unsuccessful leading to dialysis termination, after ruling out and/or correcting modifiable factors [28] or

3 or more consecutive episodes of intradialytic SBP reduction of at least 20mmHg to less than 100 mmHg, with symptom, in which nursing interventions were unsuccessful leading to dialysis termination (after ruling out and/or correcting modifiable factors [29].

Anemia, defined as hematocrit < 33% [30].

Hypoalbuminemia, defined as serum albumin < 35mg/Dl [31].

Dialysis dose (kt/V), classified as normal (at least 1.2), low (0.9-1.1) and, very low (less than 0.9) [10].

Hypertension associated CKD, defined as long standing hypertension complicated by kidney disease, common in elderly and late middle age [27].

Chronic glomerulonephritis, defined as kidney disease complicated by hypertension, common in the young and in early middle age, with or without antecedent history of pharyngitis or skin sepsis [27]

Statistical analysis

Data was analyzed using SPSS version 22.0 (IBM, CA, USA). Continuous variables were presented as means and compared using t-test while categorical variables presented as

proportions were compared using Chi square test or fisher's exact test for variables less than five. A P-value less than 0.05 was considered statistically significant. Variables with P-value less than 0.025 were entered into a multiple regression model to determine independent associates of intra-dialytic dopamine use in IDH using backward elimination to adjust for confounders [32].

Results

A total of 2968 MHD treatments for 557 [378 (67.86%) males, and 179 (32.14%) females] participants were studied. Hypertension was the commonest cause of CKD (). Sixteen (2.87%) of the participants had PDD in 50 (1.68%) of the sessions while 20 (3.59%) participants had IDD in 63 (2.12%) of the sessions. Six hundred and forty three (21.66%) sessions by 125 (22.44%) participants had intradialytic hypertension (IDHT). Five hundred and eighteen sessions (17.45%) for 108 (19.39%) participants had symptomatic IDH while 1807 (60.88%) sessions for 324 (58.17%) participants had no significant intradialytic BP changes (Table 1).

All participants had at least one comorbidity. Predialysis, hypertension was found in 2710 (91.31%) of all sessions, 421 (81.27%) of all sessions with IDH, 4 (8.0%) of sessions with PDD and 3 (4.76%) of the sessions with IDD, P=0.001. Around 8.42% of all sessions, 23.94% of all sessions with IDH, 40.0% of sessions with PDD and 36.51% of sessions with IDD were for diabetics, P<0.001. Around 9.66% of all sessions, 28.94% of all sessions with IDH, 38.74% of sessions with PDD and 36.22% of sessions with IDD were for participants with heart failure, P=0.004. The 557 participants had a total of 1644 hospitalizations within the three years of dialysis treatment (mean 0.98 ± 0.13/participant/yr). The 72 participants with IDH without dopamine had 212 hospitalization (0.98 ± 0.15/participant/yr), the 16 with PDD had 46 hospitalization (0.95 ± 0.11/participant/yr) while the 20 participants with IDD had 58 hospitalizations (0.96 ± 0.13/participant/yr), P=0.08

Fifty (9.65%) of the symptomatic IDH sessions had predialysis dopamine while 63 (12.16%) had intradialytic dopamine. The mean age of all participants, participants with IDHT, those without significant BP change, those with PDD, and those with IDD were 50.73 ± 6.51 years, 49.63 ± 7.5 years, 53.8 ± 8.43 years, 64.48 ± 8.22 years and 64.64 ± 10.31 years respectively, P=0.001.

Table 1: Sociodemographic characteristics of study population

Variables	All sessions N=2968 (%)	All sessions with IDH N=518 (%)	IDH no dopamine N=405 (%)	Sessions with PDD N=50 (%)	Sessions with IDD N=63 (%)	P–value
Sex						
Males	2033 (68.50)	298 (57.53)	238 (58.77)	26 (52.00)	34 (53.97)	0.02
Females	935 (31.50)	220 (42.47)	167 (41.23)	24 (48.00)	29 (46.03)	
Ages, years						
16-39	673 (22.68)	61 (11.78)	52 (12.84)	3 (6.0)	6 (9.52)	0.03
40-64	1771 (59.67)	298 (57.53)	241 (59.51)	26 (52.0)	31 (49.21)	
>65	524 (17.65)	159 (30.69)	112 (27.65)	21 (42.0)	26 (41.27)	
Etiology of CKD						
Hypertension	1315 (44.31)	169 (32.63)	136 (33.58)	15 (30.0)	18 (28.57)	0.05
CGN	1057 (35.61)	135 (26.06)	119 (29.38)	7 (14.0)	9 (14.29)	
Diabetes	250 (8.42)	124 (23.94)	81 (20.0)	20 (40.0)	23 (36.51)	
Others	346 (11.66)	90 (17.37)	69 (17.04)	8 (16.0)	13 (20.63)	
Dialysis/week						
1	616 (20.76)	135 (26.06)	93 (22.96)	18 (36.0)	24 (38.10)	0.03

2	1726 (58.15)	323 (62.36)	263 (64.94)	28 (56.0)	32 (50.79)	
3	626 (21.09)	60 (11.58)	49 (12.10)	4 (8.0)	7 (11.11)	
Erythropoietin/week						
1	659 (22.20)	172 (33.20)	125 (30.87)	21 (42.0)	26 (41.27)	0.06
2	1733 (58.39)	295 (56.95)	239 (59.01)	25 (50.0)	31 (49.21)	
3	576 (19.41)	51 (9.85)	41 (10.12)	4 (8.0)	6 (9.52)	
Antihypertensive drugs						
1	574 (19.34)	129 (24.90)	54 (13.3)	34 (68.0)	41 (65.1)	0.003
2	1201 (40.46)	205 (39.58)	172 (42.5)	15 (30.0)	18 (28.6)	
3	1193 (40.20)	184 (35.52)	179 (44.2)	1 (2.0)	4 (6.3)	

IDH-intradialytic hypotension, PDD-predialysis dopamine, IDD-intradialytic dopamine, CKD-chronic kidney disease, CGN-chronic glomerulonephritis.

The mean predialysis SPO_2, pulse rate, systolic, and diastolic BP were higher in sessions with PDD treatment compared to IDD treatment, P=0.06, P=0.001, P<0.001 and P=0.001 respectively (Table 2). The mean post-dialysis SPO_2, pulse rate, systolic, and diastolic BP were higher in sessions with pre-dialysis dopamine treatment compared to IDD treatment, P=0.07, P=0.05, P=0.04 and P=0.05 respectively.

Table 2: Peri-dialysis clinical findings in participants

Variables	All sessions with IDH N=518 Mean ± SD	IDH, no dopamine N=405 Mean ± SD	Sessions with PDD N=50 Mean ± SD	Sessions with IDD N=63 Mean ± SD	P-value

Predialysis $SPO_{2,}$ %	96.61 ± 13.26	96.89 ± 12.61	95.81 ± 9.46	95.62 ± 17.28	0.06
Postdialysis $SPO_{2,}$ %	96.94 ± 9.29	97.16 ± 16.41	96.48 ± 8.26	96.27 ± 11.24	0.07
Predialysis pulse, b/min	84.55 ± 7.92	82.99 ± 9.34	90.14 ± 8.26	88.63 ± 8.40	0.001
Postdialysis pulse, b/min	89.74 ± 6.47	89.68 ± 7.72	90.20 ± 7.31	91.97 ± 6.63	0.05
Predialysis SBP, mmHg	121.71 ± 9.22	126.37 ± 9.59	108.64±12.15	98.18 ± 10.31	<0.001
Postdialysis SBP, mmHg	115.42 ± 9.01	114.78 ± 8.67	116.58 ± 5.79	118.64 ± 6.50	0.04
Predialysis DBP, mmHg	78.32 ± 8.62	78.75 ± 7.35	79.63 ± 7.42	74.49 ± 6.65	0.001
Postdialysis DBP, mmHg	70.11 ± 6.61	69.76 ± 6.37	70.54 ± 8.54	71.87 ± 5.43	0.05

PDD-predialysis dopamine, IDD-intradialytic dopamine, SPO_2-oxygen saturation, SBP-systolic blood pressure

The BFR, ultrafiltration volume and dialysis duration were higher in sessions with predialysis dopamine treatment compared to intra-dialytic dopamine treatment, P=0.002, P=0.03 and P=0.04 respectively (Table 3).

Table 3: Prescribed dialysis for study population

Variables	All sessions with IDH N=518 (%)	IDH, no dopamine N=405 (%)	Sessions with PDD N=50 (%)	Sessions with IDD N=63 (%)	P-value
Blood flow rate, ml/min					
<300	128 (24.71)	94 (23.21)	13 (26.0)	21 (33.33)	0.002
>300	390 (75.29)	311 (76.79)	37 (74.0)	42 (66.67)	
Ultrafiltration volume, L					
<2	136 (26.25)	87 (21.48)	21 (42.0)	28 (3.17)	0.03
≥2	382 (73.75)	318 (78.52)	29 (58.0)	35 (55.56)	
Dialysis duration, hrs					
<4	18 (3.47)	15 (3.70)	1 (2.0)	2 (3.17)	0.04
4	500 (96.53)	390 (96.30)	49 (98.0)	61 (96.83)	
Vascular access					
Arteriovenous fistula	63 (12.16)	50 (12.34)	6 (12.0)	7 (11.11)	0.004
Tunneled IJVC	229 (44.21)	178 (43.95)	24 (48.0)	27 (42.86)	
Non-tunneled IJVC	47 (9.07)	39 (9.63)	4 (8.0)	4 (6.35)	
Femoral	179 (34.56)	138 (34.08)	16 (32.0)	25 (39.68)	

IDH-interdialytic hypotension, PDD-predialysis dopamine, IDD-intradialytic dopamine, IJVC-internal jugular vein catheter.

Dialysis termination and intradialytic death were commoner in sessions with IDD compared to sessions with PDD, P=0.001 and P=0.002 (Table 4). The dialysis dose was higher in sessions with PDD treatment compared to sessions with IDD treatment, P<0.001.5

Table 4: Intradialytic events and outcome in the study population

Variables with IDH	All session no dopamine 518 (%)	IDH, no with PDD N=405 (%)	Sessions with IDD N=50 (%)	Sessions N=63 (%)	P-values
Dialysis termination	18 (3.47)	15 (3.70)	1 (2.0)	2 (3.17)	0.001
Intradialytic death	6 (1.16)	5 (1.23)	0 (0.0)	1 (1.59)	0.002
Dialysis dose, Kt/V					
<0.9	205 (39.57)	85 (21.0)	7 (14.0)	14 (22.22)	<0.001
0.9-1.19	386 (74.52)	303 (74.81)	39 (78.0)	44 (69.84)	
>1.2	26 (5.02)	17 (4.20)	4 (8.0)	5 (7.94)	

IDH-intradialytic hypotension, PDD-predialysis dopamine, IDD-intradialytic dopamine

Predialysis dopamine was commoner in females, advancing age and diabetes, P=0.08, P=0.93 and P=0.06 (Table 5). Participants with IDD treated sessions had more frequent dialysis sessions and erythropoietin treatment, P=0.003 and P=0.04, presented for dialysis with lower blood pressures, P<0.001 and P=0.03 and were less likely to receive dialysis treatment with an AVF, P=0.08.

Table 5: Relationship between participants' variables and phase of dopamine treatment

Variables	PDD N=50 (%)	IDD N=63 (%)	OR	95% CI	P-value
Sex					
Males	26 (43.33)	34 (56.67)	1.01	0.87-1.11	0.08
Females	24 (45.28)	29 (54.72)			
Age, yrs					
<65	29 (43.95)	37 (56.06)	0.96	0.88-0.97	0.93
≥65	21 (44.68)	26 (55.32)			
Diabetes					

Yes	20 (46.51)	23 (53.49)	1.43	1.36-2.68	0.06
No	30 (42.86)	40 (57.14)			
Antihypertensives					
1	34 (45.33)	41 (54.67)	1.19	0.78-1.69	0.06
≥2	16 (42.11)	22 (57.89)			
Sessions/week					
<3	46 (45.10)	56 (54.90)	3.25	1.27-4.47	0.003
3	4 (36.36)	7 (63.64)			
Erythropoietin/week					
<3	46 (44.66)	57 (55.34)	2.01	0.67-2.04	0.04
3	4 (40.0)	6 (60.)			
Predialysis systolic hypertension					
Yes	18 (54.55)	15 (45.45)	5.97	3.68-7.83	<0.001
No	32 (40.0)	48 (60.0)			
Predialysis diastolic hypertension					
Yes	24 (48.98)	25 (51.02)	3.11	2.74-5.66	0.003
No	26 (40.63)	38 (59.37)			
Blood flow rate					
<300	13 (38.24)	21 (61.76)	3.07	1.59-4.27	0.003
≥300	37 (46.84)	42 (53.16)			
Ultrafiltration volume, L					
<2	21 38.24)	28 (57.14)	1.13	1.09-3.01	0.07
≥2	29 (45.31)	35 (54.69)			

Dialysis duration, hrs					
<4	1 (33.33)	2 (66.67)	4.42	2.22-6.04	0.001
4	49 (44.55)	61 (55.45)			
Vascular access					
AVF	6 (46.15)	7 (53.85)	1.06	1.04-1.51	0.08
Non-AVF	44 (44.0)	56 (56.0)			
Vascular access					
Tunneled IJVC	24 (47.06)	27 (52.94)	2.31	1.48-2.96	0.01
Non-tunneled IJVC	26 (41.96)	36 (58.06)			
Dialysis termination					
Yes	1 (33.33)	2 (66.67)	5.47	1.89-5.86	<0.001
No	49 (44.55)	61 (55.45)			
Intra-dialytic death					
Yes	0 (0.0)	1 (100.0)	12.3	5.33-16.92	<0.001
No	50 (44.64)	62 (55.36)			
Dialysis dose, Kt/V					
<1.2	46 9 (44.23)	58 (55.77)	0.95	0.83-0.98	1.10
>1.2	4 (44.45)	5 (55.55)			

PDD-predialysis dopamine, IDD-intradialytic dopamine, AVF-arteriovenous fistula, IJVC-internal jugular vein catheter

From multiple regression analysis (Table 6), lower predialysis systolic, and diastolic BP, shorter dialysis duration, dialysis termination and intra-dialytic death were independently associated with intradialytic dopamine treatment of IDH.

Table 6: Multivariate analysis showing independent associates of predialysis dopamine

Variables	aOR	95% CI	P-value
Dialysis frequency	1.36	1.06-2.11	0.05
Predialysis systolic hypertension	6.38	2.49-9.48	<0.001
Predialysis diastolic hypertension	2.97	2.42-4.95	0.04
Blood flow rate	2.88	1.49-3.81	0.05
Dialysis duration	3.91	0.85-4.37	0.004
Tunneled IJVC	2.02	1.45-2.35	0.07
Dialysis termination	6.06	3.59-10.73	<0.001
Intra-dialytic death	14.26	3.82-17.62	<0.001

aOR-adjusted odds ratio, CI-confidence interval, IJVC-internal jugular vein catheter

Discussion

We found the incidence of intra-dialytic hypotension, severe IDH with intra-dialytic systolic BP less than 90mmHg (for which PDD was used), and severe IDH with intra-dialytic systolic BP reduction of at least 20mmHg (for which IDD was used) were 17.45%, 9.65% and 12.16% respectively. Women and the aged were more likely to received dialysis treatments with predialysis dopamine (PDD) and, sessions with PDD had higher predialysis blood pressures, blood flow rate, ultrafiltration volume, dialysis duration, dialysis dose and lower episodes of complications such as dialysis termination, hospitalization and intra-dialytic death.

The 17.45% incidence rate of symptomatic IDH in this study mirrors findings by Sands et and falls within the wide range reported in previous studies and even within the narrower ranges reported in studies that used, similar to this study, the European Best Practices Guidelines (EBPG) criteria. Kuipers et al using the EBPG criteria, found a prevalence of 21.4% [2, 4]. In this study, the higher frequency of severe IDH using the systolic BP reduction of at least 20 mmHg compared with that of severe IDH using the nadir systolic BP less than 90 mmHg, is similar to findings by Kuipers 2016 and Flythe et al, who in separate studies, found frequencies of 21.4% and 9.2% and 50-69% respectively [4, 28]. Kuipers et al, found in another study, 3 years later, a higher prevalence of IDH using a nadir systolic BP less than 90 mmHg (11.6%) compared to the 10.1% using the systolic BP reduction of at least 20 mmHg by the EBPGs [29]. Due to the very high likelihood of attaining the intradialytic systolic BP reduction of 20 mmHg whenever the intradialytic systolic BP is less than 90 mmHg (and not viz visa), it can reliably be inferred that the nadir BP less than 90mmHg is a more severe form of IDH. This is in agreement with findings that associated higher mortalities in patients who meet the systolic BP less than 90 mmHg compared to the systolic BP reduction of at least 20mmHg [28].

The fact that dialysis sessions with the PDD had more severe IDH was further confirmed by the frequencies of PDD in females and the elderly, a pair that is well reported to be risk factors for the occurrence and severity of IDH [33]. Since the elderly are expected to have higher frequencies and severity of IDH occasioned by poor cardiac reserve (with or without left ventricular hypertrophy), the higher predialysis BP in participants with PDD reflects the predialytic inotropic support that was sustained through [34].

The marginal reductions in the hospitalization of participants with PDD compared to those with IDD, further buttresses the relative advantage of PDD therapy over the IDD. This is more so

considering the fact that participants with PDD were more likely to have poorer hemodynamic stability associated with worse systolic, with or without diastolic dysfunction as shown by their worse mortality profile [28, 35]. The higher dialysis dose in cohorts with PDD despite having worse hemodynamic and cardiovascular profile only reflect the importance of sustained low dose inotropic support in dialysis that led to higher BP which allowed for higher BFR, ultrafiltration rate and dialysis duration [36].

The higher dialysis dose in cohorts with PDD is expected to lead to better QOL, lesser hospitalization and better fluid and BP. The higher BP in the PDD cohorts allowed for higher BFR and ultrafiltration rates, both surrogate markers of higher dialysis doses as widely reported in previous studies [5, 23, 37]. Similarly, the longer dialysis duration in sessions with PDD reflects the lower incidence of dialysis termination in the PDD cohorts [38]. Although we didn't seek to study the outcome of dopamine treatment in this study, lesser dialysis termination (a pointer to reductions in the frequencies of IDH, myocardial ischemia and stunning) in the PDD cohorts would further add to the advantages of PDD over IDD [39].

The greater increases in the pulse rate with a concurrent fall in BP following dialysis in cohorts who had IDD treatment compared to cohorts with PDD is also a pointer to the relative advantages of PDD treatment [40]. Narrow and wide intradialytic variations in BP, even without symptoms, have both be reported to induce ischemic changes in the organ/systems that may lead to myocardial stunning and infarction, and further diminution of kidney function [4, 41]. The maintenance of a narrow intradialytic pulse, and blood pressure gradient, as was found in the PDD treated cohorts in this study, goes a long way in minimizing the ischemic tissue injury associated with the dialysis procedure [42]. Apart from preventing IDH and dialysis termination, optimal intradialytic BP control ensures the distribution of an effective blood volume, leading to

improved cardiac output and improved renal perfusion which is needed to optimize the contributory part of the residual kidney function in achieving higher dialysis dose as was found in cohorts with PDD in this study [44]. Considering the fact that many of the adverse effects of dopamine use is predicated on tachycardia which cause increased myocardial oxygen demand and ischemia, it becomes imperative to, not only prevent/minimize tachycardia, but also to maintain a narrow intradialytic gradient even within normal values [45, 46]. The greater risk of intradialytic death in the IDD treated cohorts could also be explained on the basis of the wider intradialytic pulse gradient. The poor diastolic filling associated with tachycardia only worsens the cardiac ischemia which if severe and/or prolonged, could induce arrhythmogenic discharges some of which could be malignant and fatal as was seen in one of the IDD cohorts [47]. This is particularly so with background cardiac systolic and diastolic dysfunction [8].

Limitations

Limitations encountered that needed to be address in future studies include single center and retrospective design of the study. Some measures targeted at reducing the frequency of IDH like sodium profiling and increasing dialysate calcium concentration among others were not routinely carried out, particularly sodium profiling which has a tendency of worsening the poor BP and fluid control that is associated with the under-dialysis that is prevalent in LINs [5, 37]. We didn't seek to estimate the residual kidney function and its contribution to the dialysis dose. Symptom reportage being subjective, its reliability in diagnosing IDH could be compromised. Cardiac enzymes were not assayed and the blood PH, despite being the best assessment tool for acid base balance was not determined.

Conclusion

The prevalence of IDH was 17.45%, of severe IDH using a nadir systolic BP less than 90 mmHg was 12.28%, and of severe IDH using a minimum 20 mmHg fall in systolic BP was 17.65%. Severe IDH that was managed with PDD was common in women while severe IDH managed with IDD was common in males. The intradialytic increases in pulse rate along with reductions in BP were more in IDD treated cohorts. Dialysis termination and intradialytic death were common in IDD treated cohorts. Predialysis low dose dopamine treatment of IDH allows for a relative optimization of the prescribed dialysis, with higher dialysis dose, and reductions in the frequencies of complications such as dialysis termination, hospitalization and intradialytic death compared with IDD treatment. Further studies with larger sample size would be needed to determine the long term effect of dopamine treatment in dialysis.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

References

1. Rhee SY, Song JK, Hong SC, Choi JW, Jeon HJ, Shin DH, et al. Intradialytic exercise improves physical function and reduces intradialytic hypotension and depression in hemodialysis patients. *Korean J Intern Med* 2019; 34: 588–598

2. Sands JJ, Usvyat LA, Sullivan T, Segal JH, Zabetakis P, Kotanko P, et al: Intradialytic hypotension: frequency, sources of variation and correlation with clinical outcome. Hemodial Int 2014; 18: 415–422 10.1111/hdi.12138

3. Wang KM, Sirich TL, Chang TI. Timing of blood pressure medications and intradialytic hypotension. *Semin Dial* 2019; 32: 201–204

4. Kuipers J, Oosterhuis JK, Krijnen WP, Dasselaar JJ, Gaillard CAJ, Westerhuis R, et al: Prevalence of intradialytic hypotension, clinical symptoms and nursing interventions - a three-months, prospective study of 3818 haemodialysis sessions. BMC Nephrol 2016; 17, 21 10.1186/s12882-016-0231-9

5. Uduagbamen PK, Ogunkoya JO, Nwogbe CI, Eigbe SO, Timothy OR. Ultrafiltration Volume: Surrogate Marker of the Extraction Ratio, Determinants, Clinical Correlates and Relationship with the Dialysis Dose J Clin Nephrol Ren Care 2021; 7: 068 10.23937/2572-3286.1510068

6. Assimon MM, Wang L, Flythe JE. Cumulative exposure to frequent intradialytic hypotension associates with new-onset dementia among elderly hemodialysis patients. Kidney Int Rep 2019; 4: 603–606 10.1016/j.ekir.2019.01.001

7. Shafi T, Mullangi S, Jaar BG, Silber H. Autonomic dysfunction as a mechanism of intradialytic blood pressure instability. *Semin Dial* 2017; 30: 537–544

8. MacEwen C, Sutherland S, Daly J, Pugh C, Tarassenko L. Relationship between hypotension and cerebral ischemia during hemodialysis. *J Am Soc Nephrol* 2017; 28: 2511–2520

9. Gul A, Miskulin D, Harford A, Zager P. Intradialytic hypotension. *Curr Opin Nephrol Hypertens* 2016; 25: 545–550

10. Lee WC, Lee YT, Li LC, Ng HY, Kuo WH, Lin PT, et al. The Number of Comorbidities Predicts Renal Outcomes in Patients with Stage 3–5 Chronic Kidney Disease J Clin Med. 2018 Dec; 7(12): 493. doi: 10.3390/jcm7120493

11. Hill N.R., Fatoba S.T., Oke J.L., Hirst J.A., O'Callaghan C.A., Lasserson D.S, et al. Global prevalence of chronic kidney disease—A systematic review and meta-analysis. *PLoS ONE*. 2016;11:e0158765. doi: 10.1371/journal.pone.0158765

12. Daugirdas JT. Intradialytic hypotension and splanchnic shifting: Integrating an overlooked mechanism with the detection of ischemia-related signals during hemodialysis. *Semin Dial* 2019; 32: 243–247

13. Collins A.J., Li S., Gilbertson D.T., Liu J., Chen S.C., Herzog C.A. Chronic kidney disease and cardiovascular disease in the Medicare population: Management of comorbidities in kidney disease in the 21st century: Anemia and bone disease. *Kidney Int. Suppl.* 2003;243:24–31. doi: 10.1046/j.1523-1755.64.s87.5.x

14. Onofriescu M, Hogas S, Voroneanu L, Apetril M, Nistor I, Kanbay M, et al. Bioimpedance-guided fluid management in maintenance hemodialysis: a pilot randomized controlled trial. *Am J Kidney Dis* 2014; 64: 111–118

15. Tepel M, Hopfenmueller W, Scholze A, Maier A, Zidek W. Effect of amlodipine on cardiovascular events in hypertensive haemodialysis patients. *Nephrol Dial Transplant.* 2008;23(11):3605–3612.

16. Kitchlu A, Clemens K, Gomes T, Hackam DG, Juurlink DN, Mamdani M, et al. Beta-blockers and cardiovascular outcomes in dialysis patients: a cohort study in Ontario, Canada. *Nephrol Dial Transplant.* 2012; 27(4):1591–1598

17. Brunelli SM, Cohen DE, Marlowe G, Wyck DV. The impact of midodrine on outcomes in patients with intradialytic hypotension. Am J Nephrol 2018; 48: 381–388 10.1159/000494806.

18. Anand U, Bastani B, Dhanraj P, Ballal SH. Intradialytic dobutamine therapy in maintenance hemodialysis patients with persistent hypotension Am J Nephrol 1999; 19: 459-463 10.1159/000013498

19. Razeghi E, Dashti-Khavidaki S, Nassiri S, Abolghassemi R, Khalili H, Nazari SSH, et al: A randomized crossover clinical trial of sertraline for intradialytic hypotension. Iran J Kidney Dis. 2015; 9:323–330 PMID: 26174461

20. Vannorsdall MD, Hariachar S, Hewitt LA: A randomized, placebo-controlled, phase 2 study of the efficacy and safety of droxidopa in patients with intradialytic hypotension. Postgraduate Medicine. 2015; 127:133–143. 10.1080/00325481.2015.1015393

21. Kanbay M, Yilmaz S, Dincer N, Ortiz A, Sag AA, Covic A, et al: Antidiuretic hormone and serum osmolarity physiology and related outcomes: what is old, what is new, and what is unknown? J Clin Endocrinol Metab 2019; 104: 5406–5420 10.12.10/JC.2019-01049

22. Chen J-F, Eltzschig HK, Fredholm BB: Adenosine receptors as drug targets — what are the challenges? Nature reviews. Drug discovery. 2013; 12:265–286 10.1038/nrd3955

23. Chiu WY, Chang H-R, Lin Z-Z, Halim E, Lian E. Intradialytic Dopamine in Maintenance Hemodialysis Patients with Persistent Hypotension. Acta Nephrologia 2007; 21: 22-29 10.6221/AN2012

24. Marinosci GZ,^ Robertis ED,^ Benedictis GD, Piazza O. Dopamine Use in Intensive Care: Are We Ready to Turn it Down? Transl Med Unisa 2012; 4: 90-94.

25. National Kidney Foundation: KDOQI Clinical Practice Guideline for Diabetes and CKD: 2012 update. Am J Kidney Dis. 2012; 60: 850-886

26. Francis GS, Bartos JA, Adatya S: Inotropes. Am Coll Cardiol 2014; 27; 63:2069-2078 10.1016/j.jacc.2014.01.016

27. Meyring-Wosten A, Zhang H, Ye X, Fuertinger D, Chan L, Kappel F, et al. Intradialytic hypoxaemia and clinical outcomes in patients on haemodialysis. Clin J Am Soc Nephrol (CJASN). 2017; 30: 464-72 10.2215/CJN.08510815

28. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. J Am Sci Nephrol 2015; 26: 724–734 10.1681/ASN.2014020222

29. Kuipers J, Vermboom LM, Iperma KJR, Paans W, Krijnen WP, Gaillard CAJM. The prevalence of intradialytic hypotension in patients on conventional hemodialysis: a systematic review with meta-analysis. Am J Nephrol 2019; 49: 497–506 10.1159/000500877

30. Panwar B, Gutierrez OM: Disorders of Iron Metabolism and Anemia in Chronic Kidney Disease. Seminars Nephrol 2016; 36: 252-261 10.1016/j.semnephrol.2016.05.00222.

31. Kora M, Tawfeek A, El-Zorkany K, AbdEl-Mohsen AH. The Relationship between Hypoalbuminemia and Intradialytic Hypotension in Haemodialysis Patients. J Kidney 2018; 4: 1 10.4172/2472-1220.1000165

32. Hosmer DW, Lameshow S. Applied Logistic Regression. 2nd ed. Wiley: New York N.Y.; 2000. p. 95.

33. Uduagbamen PK, Kadiri S: Intradialysis hypotension and hypertension in patients with end stage kidney disease in Nigeria: risk factors and clinical correlates. Ghana Med J 2021; 55: 34-42 10.4314/gmj.v55i1.6

34. Delval F, Dine T, Brunet C, Luycky M, Gressier B, Cazin C, et al. Effect of dialysis on exogenous dopamine in haemodialysed critically ill patients 1996; 21(3): 165-71 10.1111/j.1365-2710.1996.tb00017.x.

35. Tozawa, M., Iseki, K. & Fukiyama, K. Prevalence of hospitalization and prognosis of patients on chronic dialysis. *Clin Exp Nephrol* 2000; 4**,** 236–240 (2000). doi.org/10.1007/s101570070028

36. Uduagbamen PK, Samuel O. Ajayi SO, Folasade O. Soyinka FO, Kadiri S. Impact of Metabolic Acidosis on the Dialysis Dose: Findings from a two center cross-sectional study in a low income population setting. Afr J Health Sci 2021; 34(3): 329-341

37. Okaka EI, Okwuono CG: Blood Pressure Variation and Its Correlates among Patients Undergoing Hemodialysis for Renal Failure in Benin City, Nigeria Ann Afri Med 2017; 16: 65-69 10.4103/aam.aam_29_16

38. Gullapudi VRL, Kazmi I, Selby NM: Techniques to improve intradialytic haemodynamic stability. Curr Opin Nephrol Hypertens 2018; 27: 413–419 10.1097/MNH.0000000000000449

39. Flythe JE, Kimmel SE, Brunelli SM: Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. Kidney Int 2011; 79: 250–257 10.1038/ki.2010.383

40. Park J, Rhee CM, Sim JJ, Kim YL, Ricks J, Streja E, et al. A comparative effectiveness research study of the change in blood pressure during hemodialysis treatment and survival. *Kidney Int.* 2013; 84(4):795–802

41. Assa S, Hummel YM, Voors AA, Kuipers J, Westerhuis R, de Jong PE, et al. Hemodialysis-induced regional left ventricular systolic dysfunction: prevalence, patient and dialysis treatment-related factors, and prognostic significance. Clin J Am Soc Nephrol. 2012;7(10):1615–23

42. Assimon MM, Wenger JB, Wang L, Flythe JE. Ultrafiltration Rate and Mortality in Maintenance Hemodialysis Patients. Am J Kidney Dis 2016; 68: 911-922 10.1053/j.ajkd.2016.06.020

43. Liu X. · Dai C. Advances in Understanding and Management of Residual Renal Function in Patients with Chronic Kidney Disease Kidney Dis 2016; 2(4): 187-196

44. Scheeren TWL, Bakker J, Kaufmann T, Annane D, Asfar P, Boerma EC, et al: Current use of inotropes in circulatory shock Annals of Intensive Care 2021; 11, 21 10.1186/s13613-021-00806-8

45. Burton JO, Jefferies HJ, Selby NM, Mclintyre C. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol* 2009; 4: 914–920

46. Makar MS, Pun PH: Sudden Cardiac Death Among Hemodialysis Patients. Am J Kidney Dis 2017; 69: 684-695 10.1053/j.ajkd.2016.12.006