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Prevalence and Clinical Characteristics of Intradialytic Hypertension in Patients on Maintenance Hemodialysis at a Tertiary Care Center

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Aims: To estimate frequency of intra-dialytic hypertension in Indian maintenance hemdialysis patients. to describe the clinical profile of patients with intra-dialyticypertension.
Study Design: Observational descriptive study.
Place and Duration of Study: Dialysis unit Father Muller Medical College Hospital, Mangaluru Karnataka state India from 1st august 2022 to 31st July 2023.
Methodology: A minimum of 71 patients age 18 - 85 years on maintenance hemodialysis for more than 3 months previously diagnosed with hypertension - pre-dialysis blood pressure >140/90 mmhg or post-dialysis blood pressure >130/80 who are at target dry weight enrolled. weight blood pressure of each patient measured before dialysis and immediately after dialysis termination before removing dialysis access needles during six consecutive dialysis sessions. data analyzed as

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percentage for categorical variables and mean and standard deviation for continuous variables. proportions compared using chi-square test and means compared using student t test. all analysis done using SPSS software.

Results: Prevalence of intradialytic hypertension is 59.2%. IDH occurrence is significantly associated with hemdialysis frequency [p value .03], calcium channel blocking medication use [p value.009], inter-dialysis serum potassium level [p value .04], post-dialysis mean systolic blood pressure [p value .001], post dialysis mean diastolic blood pressure [value .001] occurrence of IDH is not significantly associated with gender, type 2 diabetes mellitus, age, hem dialysis vintage, pre-dialysis weight, intra-dialysis weight loss, dry weight, post-dialysis weight, pre-dialysis mean systolic blood pressure, pre-dialysis mean diastolic blood pressure.

Conclusion: Intra-dialytic hypertension results in significant morbidity mortality in maintenance hemodialysis patients. It seems multi-factorial. Interplay between dry weight, Volume overload, intra-dialysis sodium gain, intra-dialysis electrolyte disturbances, sympathetic nervous system activation, RAS renin activation, endothelial dysfunction, vessel wall stiffness, Dialysis procedure removing the dialyzable oral anti-hypertensive medication, Intravenous Erythropoietin stimulating agent ESA use and other yet unexplored factors could be operating. Long term studies on IDH in cardiovascular mortality and non access related mortality are needed.

Keywords: Intradialytic hypertension; maintenance hemodialysis; hemdialysis patients.

DEFINITIONS

Intradialytic-Hypertension: *Intra-dialysis-Hypertension is defined as the increase in Systolic Blood Pressure greater than 10mmHg from Pre- Hem dialysis to Post- hem dialysis in hypertensive maintenance hem dialysis patients in at least four of out six consecutive hem dialysis treatments.*

Dry Weight: *Dry weight is defined as the level below which further fluid removal would produce hypotension, muscle cramps, nausea, and vomiting. This weight will be decided by the treating nephrologists.*

Hypertension in Dialysis: *Hypertension in dialysis patients is defined as a midweek median intra-dialysis blood pressure greater than 140/80 mmHg.*

ABBREVIATIONS

LV - left ventricle
BP - Blood pressure
IDH - Intradialytic Hypertension
HD - hemodialysis
MHD - maintenance Hemodialysis
SBP - Systolic Blood Pressure
DBP - Diastolic blood pressure
NO - Nitric Oxide
ADMA - asymmetric di methyl arginine
ECW - extra-cellular water
ICW - Intra-cellular water
TW - total body water
TBW - total body water
IDWL - intradialytic weight loss
IDWG - interdialytic weight gain
BIA - bio impedance analysis
BIS - bioimpedance spectroscopy
RAS - renin angiotensin system
ACE - angiotensin converting enzyme
ACEI - angiotensin converting enzyme inhibitors
ARB - angiotensin receptor blocking medication

1. INTRODUCTION

The prevalence of Intradialytic Hypertension (IDH) is estimated to be around 5 to 15% in the Hemodialysis (HD) population [1]. Intra-dialytic hypertension has been associated with increased risk for short-term (6 months) and long-term (2 years) morbidity and mortality [1]. Indian data on Intradialytic hypertension is sparse [2]. We plan to estimate the frequency of IDH in Maintenance Hemodialysis [MHD] Patients and describe the clinical profile of Maintenance Hemodialysis Patients [MHD] with intradialytic hypertension [IDH].

2. REVIEW OF LITERATURE

In patients with end-stage renal disease, hem dialysis decreases blood pressure in most hypertensive patients, but some hypertensive patients show an increase in blood pressure during hem dialysis [1]. Occurrence of increase in BP pre- to post-dialysis has been identified in up to 15% of maintenance HD patients [1]. In earlier studies, participants with intra-dialysis

hypertension were older, had lower dry weight, had lower inter-dialysis weight gain, had lower serum albumin levels, and were prescribed a greater number of anti-hypertensive medications [1]. Patients with Intra-dialysis Hypertension had an increased risk of hospitalization or death compared with patients with SBP which decreased with Hem dialysis [1]. Intra-dialysis hypertension is managed with volume management by decreasing dry weight, inhibition of the sympathetic nervous system with beta-adrenergic antagonist drugs etc. [1,3,4].

Intra-dialytic hypertension, IDH refers to increase in blood pressure (BP) from pre- to post- hem-dialysis HD. Accepted definitions are not there for IDH. Inrig et al. [5] adapt definition systolic BP SBP rise 10mmHg or more, Inrig et al. [6] adapt definition SBP increase 10mmHg or more in 4 out of 6 HD sessions, Amerling et al. [7], Prabhu et al. [8] adapt definition mean arterial pressure MAP rise 15mmHg or more, Cirit et al. [9] adapt definition BP that is higher at the session end than at the session onset in 50 or more percent sessions, Gunal et al. [10] adapted definition BP that exceeds initial values during 4 HD sessions in a row, Chou et al. [11] adapt definition 15 mmHg mean BP increase occurring in 8 or more of the 12 most recent hemodialysis sessions. Chen et al. [12] adapted definition intradialytic hypertension is hypertension occurring during or immediately after the dialysis procedure that appears resistant to ultra filtration UF.

Chazot and Jean [13], opine any sustained BP rise during dialysis session with BP values during and at the end of session exceeding BP values at dialysis onset without having to frame this definition with strict numbers and also patient can be normotensive at the start of dialysis but the BP rise during haemodialysis session makes the patient hypertensive during and at the end of session. Inrig et al. [5] adapt IDH definition SBP 10 or more pre to post dialysis holds same significance in heart failure patients as in other dialysis patients.

Inrig et al. [14], Kalainy et al. [15] prevalence IDH 15% to 30% of patients treated with HD, Chazot and Jean [16] IDH occurs in 10% of HD patient. Amerling et al. [7] found IDH in 8% patients, Dorhout Mees EJ [17] found IDH in 5-15% patients, Inrig et al. [18] found IDH in 12.2% large cohort patients. IDH systolic BP 10 mmHg or more from pre to post HD occurred in at least once in 90% of the patients over the course of 6 months in one study [19,20], half of the patients had IDH in 18% or less of the total HD sessions over the 6 months study period while the another half of the patients had IDH in 18% or more of the total HD sessions over the 6 month study period. 9% patients had mean increase in systolic BP 10mm or more [21,22]. This mean is calculated from sessions over 6 months. In Park et al. [23] study of 1 hundred thousand patients over 5 years, mean SBP increase 10 mmHg or more occurred in 10% patients.

Intra-dialysis hypertension is associated with increased morbidity and mortality in maintenance hem dialysis patients. Zager et al. [24] found increased mortality if IDH systolic BP SBP is over 180 and or diastolic BP DBP is over 90 mmHg, Flythe et al. [25] large variations in Blood pressure BP during HD is risk factor for increased mortality. Inrig et al. [5] found increased risk of hospitalization death [26]. IDH patients after 6 months had higher hospitalization, mortality [18,23,26]. IDH patients have poor outcomes [13]. IDH increases hospitalization mortality. Kale et al. [2] studied admissions, mortality at 6 months and at 12 months in Indian IDH patients. Chazot and Jean [13], observed survival of patients with Intra dialytic hypotension of mean systolic BP decrease of 14 mmHg is more than either 30mmHg mean systolic BP SBP decrease or any SBP increase. Chazot and Jean [13] observed heart failure patients can have low blood pressure SBP rise 10 mmHg or more, and this low BP rise increases mortality in heart failure patients whose pre-dialysis SBP is less than 120 mmHg [27,28,29]. Pre- and post- dialysis SBP DBP correlation to mortality in HD patients follows either U or J shaped curve. Van Stone et al. [30] observed low dial sate sodium 7% lower than serum causes more extracellular volume (measured using dilution techniques) removal than total fluid removed, more fluid moves from extracellular space to intracellular space- causes intra-dialytic hypotension. High dial sate sodium removed fluid from both intracellular and extracellular space such that overall extracellular fluid reduction was much lower than with hypotonic or isotonic dial sate. Bazzato et al. [31] found captopril efficient in preventing BP rise in IDH patients. Dynamic changes in cardiac output with end diastolic volume reduction during HD increase BP [9,10]. Decreasing post dialysis body weight decreased pre dialysis bp and make IDH disappear [9], prolonging ultra filtrate [UF] time and UF rate normalized the BP, increased cardiac index and ejection fraction between the start of the dialysis session and the bp zenith and

then decreased at the end of session [10]. Erythropoietin Epo triggers endothelin synthesis [32], large sodium intake in dialysis patients modified endothelium metabolism decreasing nitric oxide NO and increasing ADMA asymmetrical dimethyl arginine in the same way shear stress forces applied on endothelium had similar effect [33]. Although high dial sate sodium concentration improves dialysis tolerance it increases sodium diffusion and exposes patient to high intra dialytic sodium load [34,35,36], positive sodium balance is the mechanism causing extracellular fluid overload and hypertension in dialysis patients [34,37], lower circulating endothelial progenitor cell levels measured prior to dialysis [38], mechanism of positive dial sate to plasma sodium gradient in IDH unknown [12], increased vessel resistance pre- to post- hem-dialysis in IDH patients [11] with progressive UF removal, lesser rise in Hematocrit in IDH group compared to non IDH group [11], positive and large sodium gradient between dial sate and plasma can be mechanism causing IDH can be put forward as hypothesis [11], no difference between IDH and control groups in potassium and calcium variations [11], heart rate variability as measured by holter monitor recording absent in IDH patients whereas present in control subjects [11]. Chou et al. [11] found increased peripheral vessel resistance in IDH patients. In the same patients whose vessel resistance increased, sympathetic nervous system SNS activity (assessed by plasma catecholamines), renin angiotensin aldosterone RAS system activity did not increase [11]. In IDH patients, plasma epinephrine, non epinephrine, renin did not increase [11]. Gunal et al. [10], Raj et al. [39], El-Shafey et al. [40] found Endothelial cell derived mediators et-1 higher levels in, lower levels vasodilator nitric oxide in idh. also found low et 1 levels in intra dialytic hypotension subjects.

cultured endothelial cells stiffen associated with nitric oxide synthesis down-regulation in high sodium concentration medium [41], high extracellular sodium concentration impairs nitric oxide release, investigator hypothesized high extracellular sodium might decrease nitric oxide and increase et-1 [41]. More serum to dial sate sodium gradient removed less intracellular fluid as measured with whole body bioimpedance spectroscopy [42] in HD patients sodium balance becomes positive when sodium intake exceeds sodium removal during dialysis [43]. Reassessing target weight [44] dry weight probing over several weeks in dry weight reduction in hypertension hemodialysis patients DRIP study lowered intra-dialytic BP slope and ambulatory BP [45]. Chazot and Jean [16] opined maintaining sufficient plasma volume at all times throughout dialysis procedure prevent clinically significant cardiac output reduction. Author also opined the need to study if any correlation exists between higher dial sate sodium and vasoconstriction and whether higher dial sate sodium causes vasoconstriction, and if vasopressin is the one that mediates this higher dial sate sodium causing vasoconstriction which is causing IDH [46,47]. Author also opined the need to study whether dial sate sodium that is higher than serum sodium is causing IDH. IDH patients can be fluid overloaded hemodynamic changes [16], patients with IDH can be volume overloaded [16,48,49], antihypertensive drugs removal by dialysis treatment [16] vasodilator nitric oxide levels did not change in between IDH and control HD patients. Chazot and Jean [16] opined when renin levels did not increase in IDH patients, efficiency of captopril to prevent IDH may not be due to renin angiotensin converting inhibiting mechanism but may be due to general vasodilator action of captopril. Inrig et al. [14] observed IDH occurs more frequently in patients who are older, have lower dry weights, are prescribed more antihypertensive medications, and have lower serum creatinine levels Lower flow mediated vasodilatation measured on a non haemodialysis day is observed in IDH patients. In this study et-1 levels not different between groups, nitric oxide levels not measured [6], Carvedilol changing Et-1 from pre- to post-haemodialysis is not different between IDH and non-IDH patients in the pilot study. Carvedilol significantly decreased change in ET-1 from pre- to post- haemodialysis in IDH patients, decreased ambulatory BP, improved FMD fibro muscular dysplasia, decreased the overall percentage of dialysis sessions in whom IDH occurs [50], blood pressure is high throughout dialysis in high dial sate sodium (pre dialysis serum sodium +5) compared to low dial sate sodium (pre- dial sate sodium -5) [51]. Higher ratio of extracellular water to total body water is seen in patients whose bp increased during dialysis [52]. Ratio of extracellular water ECW to total body water TBW was significantly higher in the increased blood pressure group, particularly post dialysis group [52], endothelial stiffness, volume excess, sympathetic nervous system SNS, renin angiotensin system RAS [14,53], subclinical pre dialysis fluid overload as measured by bioimpedance spectroscopy BIS is significantly associated with IDH, in this study

mean ultra filtrate UF volume is not different between IDH and non-IDH group [54], changes in endothelial cell function [48], association between dial sate to serum sodium gradient and IDH [48]. Carvedilol decreases IDH and improves endothelial cell dysfunction [20,48]. Older patients, less haemoglobin, less npcr, less urine output, less serum bicarbonate level, higher carotid femoral pulse wave velocity and carotid augmentation index, correlated with IDH. Less urine output UO patients had increased sodium level and pulse pressure. Less bicarbonate level correlated with higher carotid femoral pulse wave velocity [55]. Pre dialysis SBP, post-dialysis ECW/TW left ventricle volume is significantly associated with IDH [56], excess ultrafiltrate volume significantly associated with IDH and less nitric oxide levels, less nitric oxide levels significantly associated with IDH in this study endothelin 1 levels and ADMA level not associated with IDH [57,58]. Diabetes mellitus, CKD duration, HD vintage pre- and post- HD SBP and DBP, serum cholesterol level, significantly correlated with IDH. Age gender previous history of hypertension Frequency of HD Serum creatinine, haemoglobin, not associated with IDH. IDH prevalence higher could be because poor compliance antihypertensive drugs HD frequency two times weekly, and small sample size [59]. Pre-dialysis Systolic BP, after adjusting for gender, diabetes mellitus, HD vintage HD frequency, IDWG, serum cholesterol, types of anti-hypertensive drugs is significantly associated with HD. Bilateral renal artery stenosis cause of refractory IDH in a case report [60]. Target weight has to kept above dry weight flythe [61] age, duration of HD, ESA, amount of antihypertensive drugs not associated with IDH, while dry weight gain, UF goal volume statistically significantly associated with IDH [62]. Prabhu et al. [8] observed type2 diabetes mellitus, undernourishment, inter-dialytic weight gain greater than 3 kg, dialysis vintage greater than 3 years significantly associated with IDH. Prasad et al. [63] observed IDH Tend to occur in older age, lower serum albumin, lower kt/v, lower body mass index, greater use of antihypertensive medication. Prasad et al. [63] observed IDH is seen in normal, low and high –volume status, Prasad et al. [63] opined could be because greater refilling from interstitial space in fluid overloaded patients. Factors that increase total peripheral resistance especially in those with vessel stiffness cause IDH [63,64]. Carvedilol can inhibit the release of ET-1 in endothelial cell cultures [65]. Intra dialytic hypotension associated with inadequate dialysis dose [66,67,68].

3. MATERIALS AND METHODS

3.1 Materials

3.1.1 Source of data and study setting

Patients on Maintenance Hemodialysis in Dialysis Unit, Father Muller Medical College Hospital, Mangaluru, Karnataka State, India.

3.1.2 Sample size calculation

The sample size for estimation of prevalence is calculated using

$n = z2p(1-p)/e$

$Z = _{1\text{-alpha}/2} = 1.96$ with 95% confidence Interval
P= Prevalence from Reference Study (2) =5%
e= margin of error =5%
n=71

A minimum of 71 patients will be included in the study.

3.1.3 Inclusion criteria

Age 18 - 85 years

Patients on dialysis for more than 3 months

Previously diagnosed with Hypertension - Pre-Dialysis Blood Pressure >140/90 mmHg or Post-Dialysis Blood Pressure >130/80

Patients at target dry weight

3.1.4 Exclusion criteria

Oral /intra-venous antibiotic treatment within the past one month.

Active Malignancy

Not willing to participate.

3.1.5 Study design and duration

Cross-sectional Observational Study of Hypertensive Maintenance Hem dialysis patients who fulfill the inclusion criteria undergoing Hem dialysis for 6 consecutive treatment sessions in the hem dialysis unit.

A minimum of 71 patients in between August 1, 2023 to July 31, 2023 enrolled in this study.

3.2 Methods

Patients satisfying the inclusion criteria, on arrival to the Hem dialysis Unit, seated comfortably in a chair and questioned about the pertinent clinical history and the same recorded. Latest available laboratory parameters entered in the data sheet. The weight of the patient is then recorded using an electronic weighing scale. The blood pressure measured by staff nurse/dialysis technician or a doctor. The patient is then made to lie down supine in bed. Manual BP measured and recorded using a mercury sphygmomanometer before insertion of dialysis access needles on patients on dialysis through A V Fistula. On completion of Hem dialysis, before removing access needles, post HD Blood Pressure is measured and recorded while the patient is in the supine position. The patient is allowed to stand and Post Hem dialysis Weight is checked by making the patient stand on the electronic weighing scale. For each patient, this procedure routine is repeated during the next 5 consecutive hem dialysis sessions. STATISTICAL ANALYSIS Data analyzed as percentage for categorical variables and mean and standard deviation for continuous variables. Proportions compared using chi-square test and mean compared using student t test. All analysis done using SPSS software.

4. RESULTS AND DISCUSSION

4.1 Results

Results of 71 patients were analyzed.

Frequency percentage distribution analyzed for Categorical variables.

Association of categorical variable intra dialytic hypertension to other parametric categorical variables analyzed using chi-square test, to non parametric variables using Fischer exact test.

Table 1. Categorical variables-frequency distribution percentages

Gender	female	23	male	48
HD sessions frequency/week	three	33	two	38
Loop Diuretic use yes/no	no	53	yes	18
Intra-dialysis hypertension in 4 out of 6 consecutive session	no	29	yes	42
IDH yes/no				
Type2 diabetes mellitus yes/no	no	42	yes	29
Htn hypertension yes/no	no	06	yes	65
Hypothyroidism yes/no	no	70	yes	1
IHD ischemic heart disease yes/no	no	63	yes	8
Compliance with Oral anti hypertension medication use before dialysis session yes /no	no	64	yes	7
Alpha–adrenergic receptor blocker use yes/no	no	63	yes	8
Beta adrenergic receptor blocker use yes/no	no	55	yes	16
Alpha plus beta adrenergic receptor blocker use yes/no	no	50	yes	21
RAS Renin Angiotensin System inhibitor- Angiotensin converting enzyme inhibitor	no	-	yes	-
RAS Renin Angiotensin System inhibitor -angiotensin receptor blocker ARB use yes/no	no	70	yes	1
Central sympatho-lytic Clonidine or Moxonidine use yes/no	no	40	yes	31
calcium channel blocker use yes/no	no	22	yes	49
Diltiazem use yes/no	no	70	yes	1
Direct acting vasodilator Minoxidil use yes/no	no	70	yes	1
Direct acting vasodilator Hydralazine excluding Isolazine use yes/no	no	70	yes	1
Direct acting vasodilator Hydralazine including Isolazine use yes/no	no	63	yes	8
Isosorbide dinitrate – hydralazine combination tablet use Isolazine use yes/no	no	64	yes	7

Frequency percentage distribution analyzed for Categorical variables. Male subjects are 48, percentage 67.6% while female subjects are 23 percentage 32.4%. Number of subjects having Intra-dialysis hypertension Frequency of intra-dialysis hypertension IDH found in this study 42 subjects. Percentage is 59.2%. Number of subjects not having IDH is 29 subjects. Percentage is 40.8%. Out of 71 study subjects, 42 found with IDH, 29 did not. Hem dialysis frequency number of sessions in a week- 33 subjects percentage 46.5% undergoing hem dialysis two times in a week while 38 subjects 53.5% subjects undergoing hem-dialysis three times in a week. Type 2 Diabetes mellitus frequency is present in 29 subjects. Percentage is 40.8% while 42 number of maintenance hem dialysis MHD subjects not having diabetes mellitus, percentage is 59.2%. 65 MHD subjects, percentage is 91.5%, undergoing hem-dialysis have hypertension presently or in the past, while 6 subjects 8.5% subjects do not have hyper-tension. 64 subjects, 90.1 % do not presently use any kind of oral antihypertensive medications before coming for hem-dialysis session. While 7 subjects 9.9% subjects use oral anti hypertensive medication before coming for hem dialysis. 63 subjects 88.7% subjects do not have IHD presently or in the past while 8 subjects 11.3% of MHD subjects have ischemic heart disease IHD presently or in the past. 53 subjects 74.6% subjects were not on loop diuretics while 18 subjects 25.4% subjects were on loop diuretics. 22 subjects 31% subjects were not on calcium channel blocking drugs CCB while 49 subjects 69% subjects were on calcium channel blocking drugs. 40 subjects 56.3% subjects were not central sympatho-lytic drugs while 31 subjects 43.7% subjects were on central sympatho-lytic drugs. 50 subjects 70.4% subjects were not on alpha plus beta adrenergic receptor blocking drugs while 21 subjects 29.6% subjects were on alpha plus beta adrenergic receptor blocking drugs. 55 subjects 77.5 % subjects were not on beta adrenergic receptor blocking drugs while16 subjects 22.5% subjects were on beta adrenergic receptor blocking drugs. 63 subjects 88.7% subjects were not on alpha adrenergic receptor blocking drugs while 8 subjects 11.3% subjects were on alpha adrenergic receptor blocking drugs.70 subjects 98.6% were not on Angio-tensin converting enzyme inhibiting drugs ACEI, Angio-tensin receptor blocking drugs ARB. While one subject was on Angio-tensin Receptor Blocking drug, 63 subjects 88.7% subjects were not on Hydralazine while 8 subjects 11.3% subjects were on Hydralazine. 64 subjects 90.1% subjects were not on Isolazine while 7 subjects 9.9% subjects were on Isolazine. 70 subjects 98.6% were not on Minoxidil while one subject was on Minoxidil.

Table 2. Association of each categorical variable with IDH Chi-square test /Fischer's exact test

Categorical variable	value	*P*
Gender male vs female	0.686	.41
Type 2 diabetes mellitus yes/no	1.295	.26
Hypertension yes/no	1.410	.24
Hypothyroidism yes/no	1.309	.25
IHD ischemic heart disease yes/no	3.6	.06
HD frequency/week two sessions vs three sessions	4.79	.03
Compliance Oral anti hypertension medication use before HD session compliance yes/no	2.724	.1
Alpha beta adrenergic receptor antagonist yes/no	0.093	.76
RAS inhibitor- Angiotensin converting enzyme inhibitor	-	-
RAS inhibitor - angiotensin receptor antagonist ARB	1.309	.25
Beta adrenergic receptor antagonist yes/no	0.787	.36
Central sympatho-lytic Clonidine or Moxonidine use yes/no	1.679	.19
Loop diuretic use yes/no	2.473	.12
Alpha adrenergic receptor antagonist use yes/no	0.313	.58
Calcium channel blocker use yes/no	6.853	.009
Direct acting vasodilator Hydralazine use yes/no	0.313	.58
Direct acting vasodilator Minoxidil use yes/no	0.786	.38
diltiazem	0.786	.38
Isosorbide Dinitrate-hydralazinehydrochloride Isolazine use yes/no	0.719	.4

Table 3. Mean and standard deviations are calculated for continuous variables

Continuous numerical variable	Mean	Standard deviation
Age in years	57.034	13.1930
Hemoglobin level in g/dl	10.404	1.8222
Albumin llevel in g/dl	3.823	.4867
Hemodialysis Vintage in months	48.69	41.001
Serum Creatinine level in mg/dl	9.828	2.8836
serum sodium level in mEq/L	138.32	3.541
K serum potassium level in mEq/L	5.013	.8108
Serum Bicarbonate level in mg/dl	20.455	4.0580
Serum Calcium level in mg/dl	8.203	.8457
Serum Phosphorus level in mg/dl	5.855	1.8335
Alkaline phosphotase level in mg/dl	144.69	90.206
Dry weight in Kgs	54.631	11.4019
Pre-dialysis weight in Kgs	58.4532	11.88017
post dialysis weight in Kg	55.1870	11.62593
Intra-dialysis weight loss in Kg	3.2361	0.95275
Pre- dialysis mean systolic BP in mmHg	-	-
Pre- dialysis mean diastolic BP in mmHg	-	-
Post- dialysis mean systolic BP in mmHg	-	-
Post- dialysis mean diastolic BP in mmHg	-	-
Post dialysis systolic BP minus pre-dialysis systolic BP in mmHg	4.8826	19.81727
Post-dialysis diastolic BP minus pre-dialysis diastolic BP in mmHg	1.1737	6.08403

Mean age of study subjects was 57 years. Standard deviation SD +-13 years. Mean hem dialysis vintage is 48.7 months +- SD 41 months. Mean Hemoglobin level is 10.4 g/dl +- SD 1.8 g/dl. Mean albumin level in g/dl is 3.8 g/dl +- SD 0.5 g/dl. Mean serum creatinine level is 9.8 g/dl +- SD 2.9 g/dl. Mean serum sodium level is 138 mEq/L+- SD3.5 mEq/L. Mean serum potassium level is 5.0 mEq/L+-SD 0.8 mEq/L. Mean serum bicarbonate level 20.5 mg/dl. +-SD 4.0 mg/dl. Mean serum total calcium level 8.2 mg/dl+- SD 0.8 mg/dl. Mean serum phosphorus level is 5.9 mg/dl+-SD1.8 mg/dl. Mean serum alkaline phosphotase level is 145. +- SD 90. Mean dry weight is 54.3 Kilograms. +- SD 11.4 Kgs. Mean Pre-dialysis weight is 58.5 Kg+-SD11.8 Kg. Mean post dialysis Weight is 55.2 Kg+-SD11.6kg. Mean intra-dialysis weight loss is IDWL is 3.2Kg+-SD 0.95Kg.

Table 4. Association of IDH with Numerical variables analyzed using student t-test

Continuous numerical variable	Student t test value	*P*
Age in years	0.166833267000971	.87
Vintage in months	1.43571992207052	.16
Inter dialysis Hemoglobin level in g/dl	1.64650142096256	.10
Inter dialysis Albumin level in g/dl	0.665233254254108	.51
Inter dialysis Serum Creatinine level	0.173203437951382	.86
Inter dialysis Serum total calcium level	1.29624655909213	.2
Inter dialysis Serum phosphorus level	1.83525993326298	.07
Inter dialysis Serum alkaline phosphotase level	0.71744277853745	.48
Inter dialysis Serum bicarbonate level	-0.277366373997268	.78
Inter dialysis Serum sodium level	-0.229889568163969	.82
Inter dialysis Serum potassium	2.11487715207016	.04
Dry weight	1.87735000996512	.06
Pre-dialysis weight	1.79674649800867	.08
Post- dialysis weight	1.8616572180599	.07
Intra-dialysis weight loss IDWL =UF	-0.33883631060996	.74
Pre- dialysis mean Systolic BP mmHg	-0.80832883701688	.42
Pre- dialysis mean Diastolic BP mmHg	-0.226245641661444	.82
Post- dialysis mean Systolic BP mmHg	-7.98672327422955	.001
Post dialysis mean Diastolic BP mmHg	-5.17947095990307	.001

Association of each continuous parametric variable to categorical variable intra-dialysis hypertension IDH yes or no- analyzed using student t- test.

4.2 Discussion

Frequency of IDH occurrence is 59.2% in this maintenance hemodialysis [MHD] study population, while another recent single center study from south India showed prevalence 57% Prabhu RA et al [8]. IDH occurrence is not correlating with gender in this study while also not correlating with gender in Pratik Shete study [58], Mulia et al. study [62], and Mujtaba et al. [69] study. Prasad et al. [63] quote lower kt/v is associated with IDH. Raikou and Kyriaki [55] quote lower normalized protein catabolic rate nPCR, hemoglobin level and carotid- femoral pulse wave velocity c-f PWV is higher, similar kt/V for urea in IDH patients compared to patients without IDH and further quoted IDH is significantly associated with metabolic disorders including malnutrition/inflammation. Tandon et al. [70] quote short dialysis may promote sodium and volume excess, resulting in difficult to control hypertension. IDH is significantly associated with dialysis frequency number of sessions two/three per week in this study while Pratik Shete study [58] found IDH is not significantly associating with dialysis frequency. IDH occurrence is not associating with type2 diabetes mellitus in this study population while Pratik Shete [58], Prabhu et al. [8] found type2 diabetes mellitus significantly associating with IDH. Vajed et al. study [59] and also Mujtaba et al. [69] study not found correlation between IDH and type 2 diabetes mellitus occurrence. IDH occurrence is not associating with hypertension in this study population while IDH occurrence is not correlating with hypertension occurrence in Pratik Shete [58], Vajed et al. study [59], Mulia et al. study [62], and Mujtaba et al. [69] study. IDH occurrence is not correlating with Ischemic heart disease IHD occurrence in this study population while IDH occurrence is not correlating with IHD in Vajed et al. study [59], Mujtaba et al. [69] study. While Mujtaba et al. [69] study found 85.5% study population compliant with oral anti hypertensive medication, only 9.9 percent of our study population was using oral anti hypertensive medication before hem-dialysis session while the rest of them were not using. Compliance was checked by interviewing the patients. This method of checking compliance may have recall and response bias. Agarwal et al. [71] quote excessive use of antihypertensive medications may interfere with achievement of volume control. Agarwal R et al [72] quote the higher the number of antihypertensive drugs patients receive, the less likely they are to reach goal BP. In patients with volume excess, tapering of antihypertensive medications may facilitate achievement of dry weight, resulting in better control of intradialytic hypertension. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Kidney Disease Outcomes Quality Initiative [73] quote ACEI [with the exception of fosinopril] and beta blockers [particularly atenolol and metoprolol] are the anti hypertensive drug classes that are most extensively removed during dialysis. In contrast, blood concentrations of most calcium- channel blockers and Angiotensin receptor blockers ARBs are not substantially influenced by dialysis. Intra-dial tic hypertension occurrence is significantly correlating with Calcium channel blocking drug use in this study. Hem-dialysis may not remove CCBs which are among non dialyzable oral anti-hypertensive medications and therefore CCB use is able to correlate with IDH occurrence in this study while Vajed Mogal study [59] did not find significant association between calcium channel blocker use and IDH. Virdis et al. [74] quote carvedilol with vasodilating properties improve endothelial dysfunction in vivo. Saijonmaa et al. [65] quote carvedidlol block endothelin-1 release in vitro. Inrig et al. [50] quote in uncontrolled study carvedilol treatment associated with improvement in endothelium dependent flow mediated vasodilatation which wa accompanied by reduced occurrence of intradialytic hypertensive episodes and fall in 44 hour ambulatory BP. IDH occurrence is not correlating with alpha plus beta adrenergic receptor blocking drug use in this study while IDH occurrence is correlating with non dialyzable beta blockers [alpha plus beta adrenergic receptor blocking drug use in Van Buren et al. [50] study. Kubo et al. [75] quote beta blockers, at variance with alpha blockers seem to modulate rsther than evenly downregulate sympathetic activity. In patients with heart failure on ACEI, beta blocker do not reduce background sympathetic nerve discharge but restore low- and high – frequency harmonic oscillations in sympathetic nerve activity. IDH occurrence is not correlating with alpha adrenergic receptor blocking drug use in this study while IDH occurrence is not correlating with alpha adrenergic receptor drug use in Vajed Mogal [59] study, Mujtaba et al. [69] study. Converse et al. [76] quote hemodialysis doubled sympathetic nerve firing in patients with intact

native kidneys. Bilateral nephrecetomy had dramatic effect in hemodialysis patients with resistant hypertension and reduced sympathetic nerve discharge is the reason behind this hypotension effect of bilateral nephrectomy. Schlaich et al. [77] quote renal denervation decreases sympathetic nerve discharge and decreases bblood pressure in hemodialysis patients with severe hypertension resistant to drug treatment and ultrafiltration intensification. Rubinger et al. [78] quote intradialytic hypertensive episodes rather than evoking baroreceptor mediated bradycardia are accompanied bysynchronous increases in heart rate, a phenomenon underlying sympathovagal imbalance and sympathetic overactivity. McGregor et al. [79] quote ultrafiltration during dialysis activates sympathetic nervous system SNS. McGregor et al. [79] also quote reducing ultrafiltration rate and diluting volume removal over a longer dialysis treatment may attenuate SNS activation. Inrig et al. [1] quote blocking background adrenergic activity with alpha and beta blockers may improve intradialytic hypertension. Heerspink et al. [80] quote beta-blockers reduce cardiovascular morbidity and mortality in hemodialysis patients. Agarwal et al. [81] quote hypertension in hemodialysis treated with Atenolol or lisinopril HDPAL trial, occurrence of serious cardiovascular events, including myocardial infarction, stroke, and cardiovascular death, higher in the Lisinopril than in the Atenolol group. IDH occurrence is not correlating with beta adrenergic receptor blocking drug use in this study while beta adrenergic receptor blocking drug use is not associated with IDH in Vajed Mogal study [59], Mujtaba et al. [69] study. IDH occurrence is not correlating with loop diuretic use in this study while study where correlation between IDH occurrence with loop diuretic use is lacking. IDH occurrence is not correlating with central sympatho-lytics clonidine, moxonidine use in this study while IDH occurrence is not correlating with central sympatho-lytic use clonidine, moxonidine use in Vajed Mogal [59] study. IDH occurrence is not correlating with hydralazine use in this study while IDH occurrence is correlating with vasodilator use in Mujtaba et al. [69] study. Inrig et al. [1] quote excess activation of the renin–angiotensin response to rapid intravascular volume reduction during dialysis is another mechanism of intradialytic hypertension. Bazzato et al. [31] showed captopril just before dialysis in patients with intradialytic hypertension achieved adequate BP control and cessation of intradialytic hypertensive episodes. Heerspink et al. [80] ACEI ARBs reduce cardiovascular morbidity and mortality in ESRD patients, Cice et al. [82] quote ACEi ARB well suited to treat HD patienst with systolic dysfunction. Takenaka et al. [83] quote direct renin inhibition may attenuate change in intradialytic BP slopes through a more rapid suppression of RAS activity; pilot studies suggested aliskiren is effective in reducing predialytic and home BP in dialysis patirents with refractory hypertension while Correlation of IDH occurrence with Angiotensin converting enzyme inhibiting drug use Angiotensin receptor blocking drug use cannot be assessed in this study as only one patient is using this drug among this study subjects. While IDH not correlating with ACE inhibitors/ARB use in Mujtaba et al [69] study. Correlation of MRA mineral corticoid receptor antagonists on IDH occurrence is not able to study as any study patient is not using this class of drugs in this study. Correlation of thiazide diuretics and IDH occurrence could not be studied as none of this study patients are using this class of drugs. Rizzioli et al. [84] quote minoxidil formerly used for IDH with good results. minoxidil Correlation with IDH occurrence could not be analyzed for statistical significance in this study because only one patient in this study population is using this drug. While Mujtaba et al. [69] study found IDH occurrence is not correlating with vasodilator use. Boyle and Berns [85] quote ESA erythropoietin stimulating agents are associated with new- onset hypertension or worsening of pre existing hypertension in hemodialysis patients. Kang et al. [86] quote ESA may trigger acute vasoconstrictor effect mediated by endothelin-1. Intravenous human recombinant erythropoietin causeas a clinically important [around 20 mmHG] increase in mean afterial pressure after around 30 minutes of injection and such an increase lasts 3 hours. In contrast, subcutaneous ESA administration, particularl long acting do not raise BP. Intravenous ESAs are usually administered adter dialysis and therefore may hardly contribute to the intradialysis BP profile. All the study participants in this study are receiving subcutaneous ESA after dialysis termination.

Among numerical continuous variables, IDH occurrence is significantly correlating with post dialysis mean Systolic BP in our study and Pratik shete et al study [58] IDH occurrence is significantly correlating with post dialysis mean diastolic BP in this study and Pratik shete et al study.[58] IDH occurrence is not correlating with age in this study and Pratik Shete study [58], Mulia et al. study [62], while Mujtaba et al. [69]

study found is correlating with age. IDH occurrence is not correlating with hem dialysis vintage in this study, Pratik Shete study [58], also Mujtaba et al. [69] study found IDH is not correlating with vintage. IDH occurrence is not correlating with inter dialysis serum creatinine level in our study while and Pratik Shete study [59], study also found not correlating with serum creatinine level. IDH occurrence is not correlating with serum albumin level while Zou and Sun [87] found study found IDH correlating with serum albumin level. Grangé et al. [88] studied serum albumin level in MHD patients and opined the need to define intra dialysis hypertension IDH definition. IDH occurrence is not correlating with Hemoglobin level in this study while Zou and Sun et al. [87] found hemoglobin level is correlating with IDH. Pratik Shete [58] study found IDH not correlating with hemoglobin level. Grangé et al. [88] studied hemoglobin level and opined the need to define IDH hypertension definition. Song et al. [89] quote high time-averaged concentration of dialysate sodium during sodium profiled hemodialysis is associated with positive sodium balance and higher interdialytic weight gain. Flanigan et al. [90] quote sodium gain may arise even at standard dialysate sodium [ie, 140mEq/L] when patient start dialysis with a lower serum sodium concentration [ie, less than 140 mEq/L]. Movilli et al. [91] quote particular importance of positicve sodium gradient in pathogenesis of intradialytic hypertension apart from rising interdialytic weight gain and BP. They quote direct association between doalysate- to-serum sodium gradient and change in SBP during dialysis. Oberleithner et al. [41] quote high sodium concentrations blunt endothelial NO release, causing vasoconstriction and increased peripheral vascular resistance. Munoz et al. [92] quote eliminating intradialytic sodium load is a therapeutic strategy. Inrig et al. [51] quote effect of low versus high dialysate sodium concentration [5 mEq/L lower or higher than serum sodium respectively] on intradialytic BP with low dialysate sodium for 3 week period significant reduction in weakly average of intradialytic SBP. IDH occurrence is found not correlating with serum sodium level in this study while Van Buren and Inrig [93] study found difference from dial sate to serum sodium level is correlating with IDH. Dolson et al. [94] quote acute decrease in serum potassium level augment blood pressure. Low dialysate potassium associated with rebound elevation of blood pressure one hour after dialaysis. Dialysate potassium concentration between 2.0-3.5 mEq/L unlikely that hypokalemia triggered vasoconstriction and intra dialytic hypertension or post dialysis hypertension. IDH occurrence is found significantly correlating with serum potassium level in this study while Choi et al. [95] study found IDH mortality correlating with low serum potassium level. IDH occurrence is not correlating with serum bicarbonate level in this study while Grangé et al. [88] study serum bicarbonate level opined the need to define hypertension IDH. Fellner et al. [96] quote changes in ionized calcium levels acutely affect myocardaial contractility and vascular tone. Gabutti et al. [97] quote Increased dialysate calcium concentration assoiated with improevement in intradialytic hemodynamic instability. LeBeouf et al. [98] quote Increased dialysate calcium acutely worsens arterial compliance and minimizes intradialytic BP reduction. Mourad et al. [99] had significantky lower aortic pulse wave velocity than thoise with intradialytci hypertension. London et al. [100] quote arterial stiffness goes along with endothelial function in ESKD patients. Georgianos et al. [101] quote consequence of increased afrterial stiffness is premature arrival of reflected pulse wavefrom the periphersy to the aorta during systole rather than diastole, raising aortic SBP and left ventricular afteroad. A total calcium level in this study is not associated with IDH in this study while Grangé et al. [88] studied serum calcium level and opined the need to define hypertension in hem dialysis patients. IDH is found not correlating with Serum Phosphorus level in this study while Grangé et al. [88] study serum phosphorus level and opined the need to define hypertension IDH. IDH is not correlating with ideal weight in this study while Zou and Sun [87] found dry weight is correlating with IDH. Mulia et al. [62] study found is correlating with dry weight gain UF goal volume. Agarwal and Light [45] quote probing dry weight is important part of adequate volume management. All the patients in this study are at dry weight at the onset of the study. IDH is not correlating with pre dialysis weight while Ren et al. [56] study found proportion of extracellular water to total body weight (extra-cellular water ECW/ total body water TW), as evaluated by bio-impedance analysis [BIA], was significantly higher in the IDH group than in the other three groups both in pre- and post-dialysis. IDH is not correlating with post dialysis weight in this study while Zou and Sun [87] study found IDH is correlating with post dialysis weight. Mujtaba et al. [69] study found inter-dialysis weight gain is not correlating with IDH. Zou and Sun [87] found higher IDWG, % post dialysis body weight is correlating with IDH,

Prabhu et at. study [8] found IDWG more than 3 kg is found significantly associated with IDH. IDH is not correlating with pre dialysis Systolic BP in this study while Pratik Shete study [58], found IDH is correlating with pre dialysis systolic BP, Vajed et al. [59] also found pre dialysis systolic BP is found significantly associated with IDH. Mujtaba et al. [69] study found IDH is not correlating with pre dialysis systolic BP. IDH is not correlating with pre dialysis diastolic BP in this study, while Pratik Shete study [59] found IDH is correlating with pre dialysis systolic BP, Di et al. [102] case reports and Rubinger et al. [103] proof of concept study quote renal sympathetic denervation in hemodialysis patients with uncontrolled predialysis BP greater than 140/90 mmHg despite current use of atleast 3 different antihypertensive agents associated wiuth significant reductions of 28/10mmHg that persisted for a 12 month follow up period. Because background persistent hypertension is a hallmark in patients with intradialysis hypertension, these observations suggest that in severe cases, resistant to drug treatment and dialysis treatment optimization, renal denervation may be an important option to consider [104,105].

5. CONCLUSION

Intradialytic hypertension is multi-factorial. volume overload, intradialytic sodium gain, intradialytic electrolyte imbalances, SNS activation, Renin activation, Endothelin release, vessel wall stiffness, hemodialysis procedure removing the dialyzable oral antihypertensive drugs, IV ESA administration, might be operating to cause this IDH phenomeneon. Future studies exploring the relation among these variables might throw light on the underlying mechanism. IDH in this study is not significantly associated with gender, type 2 diabetes mellitus, age, hemodialysis vintage, serum creatinine level, pre dialysis weight, intra dialysis weight loss, pre dialysis mean systolic bp, pre dialysis mean diastolic BP, IDH in this study is significantly associated with post dialysis mean BP, post dialysis mean diastolic BP,inter-dialysis serum potassium level, calcium channel blocking drug use, HD frequency.

6. FUTURE DIRECTIONS AND FUTURE IMPLICATIONS

Studies on effect of malnutrition inflammation conditions including type 1 DM, type 2 DM, alcohol, smoking, substance abuse, burns, gastrointestinal fistula, gastrointestinal disease chronic liver disease, chronic encephalopathy, seizure diorder, psychoses, mood disorder, psychotropic substance abuse thyroid hormone, glucocorticoid hormone, sex steroid hormone, pituitary hormone, other endocrine disease, chronic heart failure, level of physical activity, skin fold thickness, serum potassium level, serum albumin level, haemoglobin level, HD frequency, HD vintage, dialysis dose, dry weight, ideal weight, inter-dialytic weight gain, pre-dialysis weight, intra-dialytic weight loss, post dialysis weight on IDH phenomenon. Bio-impedance spectroscopy studies on water volume movement between extracellular water, intracellular water, intravascular water compartment, changes in serum sodium concentration occurring from hour to hour during dialysis, rate of UF removal during dialysis, dialysis solution temperature, effect on IDH. Studies on dynamic echocardiography performed during the time of dialysis can shed light on the impact of changes in diastolic LV filling, end-diastolic volume, changes in systolic function, changing end-systolic volume on IDH. Studies on carotid femoral pulse wave velocity, abdominal aorta pulse wave return and impact of Calcium channel blockers, beta blockers, ACEI, ARB on vessel wall stiffness will shed light on effect of arterial compliance on IDH. Studies on sympatethic nervous system activity during dialysis, endothelial dysfunction, vasoconstriction, vasoconstrictor molecules, vasodilatation, vasodilating molecules, ADMA, NO, impact of ACEI, ARB, Calcium channel blockers, beta blockers on RAS will shed light on effect of these on IDH. Studies on loop diuretic use that can mitigate volume overloaded patients and can impact IDH occurrence are needed. studies on compliance with oral antihypertensive medication, frequency of non dialyzable oral antihypertensive medication, and its relation to IDH could be useful. Long term Studies on impact of IDH on CV related hospitalization and hard outcomes such as, cardiovascular mortality, all cause mortality, non-access related mortality are needed.

7. LIMITATIONS

Many patients not using oral anti-hypertensives medication before dialysis session is limitation in this study.

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CONSENT

Author declares that 'written informed consent was obtained from the patient for publication of this original research article.

ETHICAL APPROVAL

The research study approved by the institutional review board at father muller institutional ethics comittee, number fmmciec/ccm/537/2022, dated 28.07.2022.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have not been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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