Study of the Possible Pathogenic Role of Endothelin-1 in Intra Dialytic Hypertension and Effect of Carvedilol in Disease Improvement in Maintenance Hemodialysis Patients

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Abstract: Background: intradialytic hypertension is a common problem observed in patients on maintenance hemodialysis and considered as an independent predictor of adverse clinical outcomes. **Aim of the Work:** to study the possible pathogenic role of Endothelin-1 in intradialytic hypertension and effect of Carvedilol in disease improvement in maintenance hemodialysis patients. **Methodology:** the study is a case control study included 60 patients with end stage renal disease on maintenance hemodialysis, selected from Ain shams university hemodialysis unit during the period from March. 2016 to September 2017. Group A: 30 patients with intradialytic hypertension. Group B: 30 patients without intradialytic hypertension. All patients submitted to full history taking and clinical examination; laboratory investigations included routine investigations and estimation of Endothelin-1 post dialysis. Group A patients with intradialytic hypertension (IDH) subjected to a non controlled single blinded clinical trial, Carvedilol was given on regular basis for 4 weeks titration period (starting dose 6.25 mg BID) till maximal tolerated dose reached, then patients subjected to assessment of ET-1 level before and after dialysis to estimate the effect of Carvedilol on ET-1 level and its possible association with intradialytic hypertension improvement. **Results:** serum Endothelin-1 (ET-1) ranges between (.45-9.00pg/ml) in cases group with the mean of 1.82±1.99 in comparison to (.75-3.85pg/ml) in controls group with the mean of 1.61±1.01 with no statistically significance between both groups. Group A intradialytic hypertension patients subjected to Carvedilol have ET-1 level before and after dialysis was estimated after intake with ranges from (.75-9.0 pg/ml) pre hemodialysis with a mean of [4.25±3.13] and (.50-9.0 pg/ml) after hemodialysis with a mean of [2.84±2.41] with highly statistically significance between pre and post hemodialysis E-1 after Carvedilol. **Conclusion:** intradialytic hemodynamic changes including IDH is a complex interplay of endothelin-1, and endothelial function. Carvedilol intake shows marked improvement of Endothelin-1 level and also improvement of intradialytic hypertension.

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Keywords: Endothelin-1, Intra Dialytic Hypertension, Carvedilol, Maintenance Hemodialysis Patients

1. Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD) receiving maintenance hemodialysis**.** Intradialytic hypertension had previously been defined by arbitrary increases in systolic or mean arterial BP from pre to post dialysis. While BP decreases are the expected response, an increase in BP occurs in almost all hemodialysis patients from time to time, an increase in systolic BP of at least 10 mm Hg occurs in approximately 20% of all hemodialysis treatments [(1)]**.**

Intradialytic hypertension, is a relatively common problem observed in the maintenance HD population. Intradialytic hypertension occurs in 5–15% of end-stage renal disease patient hemodialysis [(2)]**.**

Factors that might be involved in the pathogenesis of intradialytic hypertension include the following: extra cellular fluid volume overload, activation of the renin–angiotensin–aldosterone system (RAAS), activation of the sympathetic nervous system, endothelial cell dysfunction, dialytic sodium gradient [(3)] peripheral vasoconstriction, fluctuations in electrolyte levels during dialysis, removal of antihypertensive medications by hemodialysis, and use of erythropoiesis stimulating agents.

From the view of hemodynamic profiles, peripheral resistance and cardiac output are the most important factors contributing to arterial blood pressure. Vascular endothelial cells play an important role in blood pressure regulation, because they release a variety of vasoactive substances which are involved in vasomotor regulation. Nitric oxide (NO) and endothelin-1 (ET-1), synthesized and secreted by endothelial cells, are well-known endogenous vasodilators and vasoconstrictors with mutual antagonism, which maintain normal vascular tones [(4)].

Endothelial cell dysfunction is a major cause of intradialytic hypertension and highly predictive of adverse cardiovascular outcomes [5].

In a recent study, researchers compared pre-dialysis plasma vasoactive substances with their post-dialysis levels in both intra dialytic hypertension maintance hemodialysis patients (MHD) and non-intra dialytic hypertension (MHD) patients, in order to gain insight into the role of vasoactive substances in the development of IDH., inappropriately elevated ET-1 plasma concentrations may play a predominant role in the pathogenesis of IDH [6].

However it is unknown whether pharmacologic inhibition of ET1 can abolish intradialytic hypertension. Nonspecific ET1 inhibitors (such as RAAS inhibition or Carvedilol) could potentially improve intradialytic hypertension by inhibiting ET1 release [7].

Aim of the Work

The aim of the work is to study the possible pathogenic role of Endothelin-1 in intradialytic hypertension and effect of Carvedilol in disease improvement in maintenance hemodialysis patients.

2. Patients and Methods

The present study is a case control study included 60 patients with end stage chronic kidney disease on maintenance hemodialysis with range of age from 18-65 years old at the time of our study, on regular hemodialysis thrice weekly for at least 6 months. Each dialysis session lasted four hours using bicarbonate dialysate; these patients were divided into two groups according to presence of intradialytic hypertension to **Group A:** thirty (30) patients with intradialytic hypertension (cases) 17 males and 12 females, **Group B:** thirty (30) patients without intradialytic hypertension (controls) 21 males and 9 females. This study was conducted on patients from Ain Shams University hospital hemodialysis unit during the period from March. 2016 to September 2017.

All patients were treated with heparin as anticoagulation therapy. Autogenous arteriovenous fistula and arteriovenous graft fistula served as HD access. The ultrafiltration rate was kept constant in the dialysis process, and the ultrafiltration volume matched with the pre-dialysis weight and dry weight.

A standard mercury sphygmomanometer and a cuff of proper size were used in order to measure peripheral BP at the level of brachial artery. Measurements were taken in the contralateral arm from that used for dialysis access in the sitting posture after a 10-min rest, according to guidelines. Three BP recordings with 1 hour interval between them were obtained during dialysis, and the mean of these measurements was included in our analysis. Phase I and V Korotkoff sounds were recorded for systolic BP (SBP) and diastolic BP (DBP), respectively.

Membrane material was mainly polyethersulfone with a surface area of 1.3–1.4 m^2. The reverse osmosis dialysis fluid was a sugar-free bicarbonate dialysate with 500 mL/min flow, which contained Na^+ 135 mmol/L, HCO_3^- 32 mmol/L, Ca^{2+} 1.25 mmol/L, Mg^{2+} 0.5 mmol/L, and K^+ 2.0 mmol/L, and had a temperature of 36.0–37.0°C. We used the dialysis machines, Fresenius 4008B and 4008S (Bad Homburg vor der Höhe, Germany), as well as Gambro AK200 (Stockholm, Sweden).

The informed consent was obtained from all participants. The research protocol did not interfere with any medical recommendations or prescriptions. All patients were subjected to the history taking and clinical examination. Assessment of the following parameters: body weight before and after dialysis, blood pressure, before the session directly, during (every hour) and after hemodialysis. In addition, the following laboratory investigations were done including CBC, serum Na, serum K, Iron profile (serum iron, TIBC, serum Ferritin), serum Calcium, serum Phosphorus, serum PTH level before dialysis and Estimation of Urea Reduction ratio (URR).

Intradialytic weight gain will be calculated as (IDWG; kg) = pre-dialysis weight − post-dialysis weight. Ultrafiltration rate will was calculated as (mL/h/kg) = ultrafiltration rate (mL/h)/dry weight (kg). Body mass index will be calculated as = weight/height^2 (kg/m^2) and **estimation of post dialysis Endothelin-1 (ET-1)**. ET-1 will quantitatively be measured by commercially available enzyme-linked immunoassay (R & D systems, Minneapolis, US) (detection limit 0.02 pg/ml) by Plasma (taken after dialysis) will be frozen in -80c for measurement of Endothelin-1. This Enzyme Immunoassay kit is designed to detect a specific peptide based on the principle of"competitive" enzyme immunoassay. **Group A patients** With (intradialytic hypertension) will be subjected to a non controlled single blinded clinical trial, patients will be given Carvedilol on regular basis for 4 weeks titration period (starting dose 6.25 mg BID) till maximal tolerated dose is reached (no recorded hypotensive episodes) then patients will be subjected to assessment of ET-1 level before and after dialysis to estimate the effect of Carvedilol on ET-1 level and its possible association with intradialytic hypertension improvement. Assessment of serum Na, K, Ca and Po4 before hemodialysis will take place. Changes of systolic blood pressure (SBP) and diastolic blood pressure during dialysis session after Carvedilol intake were recorded. **Exclusion Criteria Were** decompensated liver disease (liver cirrhosis), cardiomyopathic patients with decompensted heart

failure, presence of active neoplasm or active wounds or active inflammation, inability to measure BP by routine methods in the upper extremity, non compliance on dialysis modality during study period and patients with duration less than six months on regular hemodialysis.

3. Results:

This Case control Study was done in Ain Shams University Hospital hemodialysis unit. The study includes 60 prevalent hemodialysis patients, the first group is cases group (A) 30 patients with intradialytic hypertension mean of age in this group 42± 12.77 year range (18-65), female patients were 17 (56.7%) and male patients were 13 (43.3%). The second group is controls group (B) 30 patients without intradialytic hypertension with mean of age 47.67±14.44 year range 18-65, male patients were 21 (70%) and female patients were 9 (30%). Endothelin-1 (ET-1) was estimated post dialysis for all patients cases and controls included in the study, its results ranges between (.45-9.00pg/ml) in cases group with the mean of 1.82±1.99, and between (.75-3.85pg/ml) in controls group with the mean of 1.61±1.01.

Group A (intradialytic hypertension) patients subjected to a non controlled single blinded clinical trial, patients were given Carvedilol on regular basis for 4 weeks titration period (starting dose 6.25 mg BID) till maximal tolerated dose reached (no recorded hypotensive episodes), then ET-1 level before and after dialysis was estimated with the range of (.75-9.0 pg/ml) pre hemodialysis with a mean of [4.25±3.13] and (.50-9.0 pg/ml) after hemodialysis with a mean of [2.84±2.41]. It shows improvement of Endothelin-1 level after Carvedilol intake and also improvement of intradialytic hypertension. Age, gender, dry weight, body mass index (BMI), presence of comorbidities and standard pre-dialysis laboratory measures did not significantly differ between the two groups of the study.

Age, gender, dry weight, body mass index (BMI), presence of comorbidities and standard pre-dialysis laboratory measures did not significantly differ between the two groups of the study.

Table (1): Level of Post dialysis Endothelin-1 of group A (cases) and group B (controls) of the studied population:

ET-1(Group A)	**Minimum**	**Maximum**	**Mean**	**SD**	**Median (IQR)**
Post dialysis ET-1(pg/ml)	.45	9.00	1.827	1.99	1.36 (1.63)
ET-1(Group B)	**Minimum**	**Maximum**	**Mean**	**SD**	**Median (IQR)**
Post dialysis ET-1(pg/ml)	.50	3.85	1.615	1.018	1.12 (1.61)

Table 1 shows Level of Post dialysis E-1 of group A (cases) and **group B (controls)** of the studied population.

Table (2): Level of Endothelin-1 pre and post dialysis in group A (cases) after Carvedilol intake.

ET-1 level after Carvedilol intake	**Minimum**	**Maximum**	**Mean**	**SD**	**Median (IQR)**
Pre hemodialysis ET-1(pg/ml)	.75	9.00	4.25	3.13	3.55 (6.03)
Post hemodialysis ET-1(pg/ml)	.50	9.00	2.84	2.41	1.62 (4.06)

Table 2 shows the level of Endothelin-1 pre and post dialysis in cases group after Carvedilol intake.

Table (3): Blood pressure level after Carvedilol intake in group A (cases):

Blood Pressure after Carvedilol	**Minimum**	**Maximum**	**Mean**	**SD**
Systolic blood pressure (mmHg)	120	170	143.33	12.69
Diastolic blood pressure (mmHg)	70	100	85.67	6.26

Table 3 shows Systolic and Diastolic Blood pressure in cases group after Carvedilol intake.

Table (4): Comparison between group A and B according to post dialysis ET-1:

Post dialysis ET-1	**Cases (N=30)**	**Control (N=30)**	**Mann whitney test**	**p-value**
Median (IQR)	1.36(0.6)	1.12(1.61)	414	0.594

Wilcoxon Rank; p-value >0.05 NS

Table 4 shows no statistically significant difference between groups according to post dialysis ET-1.

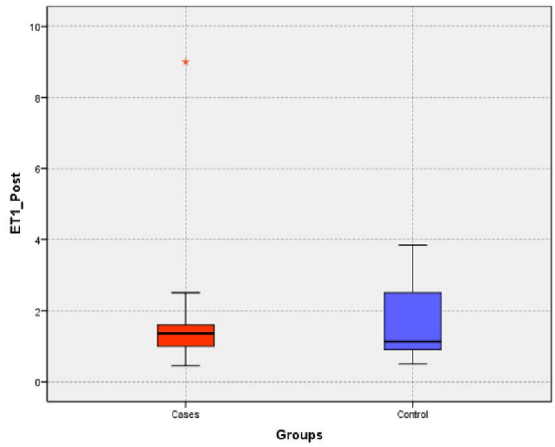

Fig. (1): Box plot between groups according to post dialysis ET-1.

Table (5): Comparison between E-1 in group A after Carvedilol intake (pre dialysis and post dialysis).

Dialysis ET-1(pg/ml)	Cases (N=30)	Median Diff.	z-test	p-value
After Carvedilol (pre dialysis ET-1)	3.55 (6.03)	1.92	3.703	<0.001**
After Carvedilol (post dialysis ET-1)	1.62 (4.06)			

z- Mann-Whitney test
**p-value <0.001 HS

Table 5 shows highly statistically significant difference between (pre dialysis ET-1) and (post dialysis ET-1) after Carvedilol intake.

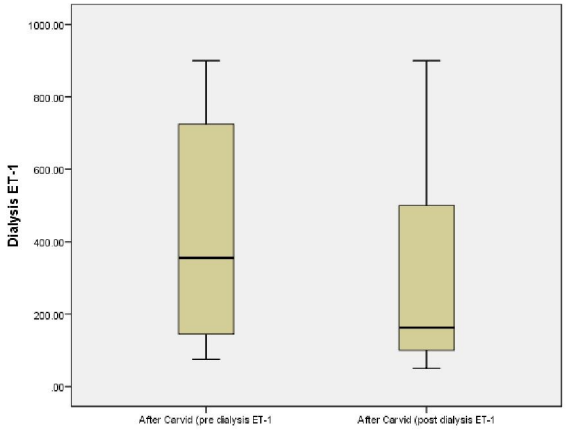

Fig. (2): Box plot between (pre dialysis ET-1) and (post dialysis ET-1) after Carvedilol in cases group.

Table (6): Comparison between group A and B according to cause of hemodialysis:

Cause of hemodialysis	Cases (N=30)	Control (N=30)	x2	p-value
Chronic glomerulonephritis	6 (20.0%)	1 (3.3%)	31.938	<0.001**
Congenital glomreulonephritis	1 (3.3%)	1 (3.3%)		
DM	1 (3.3%)	2 (6.7%)		
HTN	13 (43.3%)	0 (0%)		
Obstructive uropathy	2 (6.7%)	3 (10.0%)		
SLE	1 (3.3%)	1 (3.3%)		
Unknown cause	3 (10.0%)	21 (70.0%)		
Vesico ureteric reflux	2 (6.7%)	1 (3.3%)		
Poly cystic kidney	1 (3.3%)	0 (0%)		

x^2 Chi-square test **p-value <0.001HS

Table 6 shows high statistically significant difference between the two groups according to cause of hemodialysis.

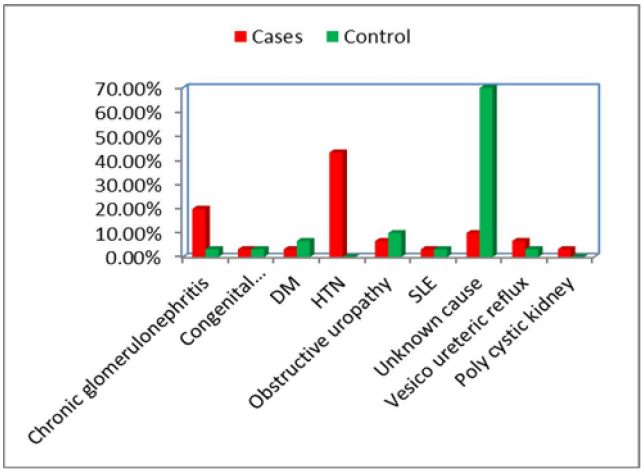

Fig. (3): Bar chart between groups according to cause of hemodialysis.

Table (7): Comparison between group A and B according to Anti-hypertensive medications:

Anti-hypertensive medications	Cases (N=30)	Control (N=30)	x2	p-value
B blocker (Carvedilol)	3 (10.0%)	0 (0%)		
Ca channel blocker & methyl dopa & Alpha blocker	2 (6.7%)	0 (0%)		
ACE I intermitant & Ca Channel blocker & methyl dopa	3 (10.0%)	0 (0%)		
ACEI & Ca channel blocker & methyl dopa & Alpha blocker	2 (6.7%)	0 (0%)		
ACEI intermittent	4 (13.3%)	0 (0%)		
B blocker intermittent	2 (6.7%)	1 (3.3%)		
Ca channel blocker	1 (3.3%)	0 (0%)	49.867	<0.001**
B blockers	0 (0%)	6 (20.0%)		
Ca channel blocker & methyl dopa	6 (20.0%)	0 (0%)		
Ca channel blocker & methyl dopa & Alpha blocker	4 (13.3%)	0 (0%)		
Ca channel blocker & methyl dopa	3 (10.0%)	2 (6.7%)		
NAD	0 (0%)	19 (63.3%)		
Ca channel blocker	0 (0%)	2 (6.7%)		

x^2 Chi-square test
**P-value <0.001HS;

Table 7 shows statistically significant difference between the two groups according to anti-hypertensive medication.

Table (8): Comparison between group A and B according to laboratory data:

Laboratory	Cases (N=30)	Control (N=30)	t-test	p-value
Na (mmol/l)	136.93±2.53	137.20±2.09	-0.445	0.658
K (mmol/l)	5.12±0.28	4.88±0.32	3.159	0.003*
Hb (g/dl)	10.49±1.65	10.75±1.44	-0.643	0.523
Urea reduction ratio	68.07±6.71	68.73±7.53	-0.358	0.721
Ca (mg/dl)	7.94±0.80	10.24±10.37	-1.212	0.231
Po4(mg/dl)	4.12±1.58	4.58±1.41	-1.207	0.232
PTH (pg/ml)	499.7±3461.98	591.07±377.77	-0.838	0.405
S. Iron (mcg/dl)	69.20±36.19	75.90±47.71	-0.613	0.542
TIBC (mcg/dl)	219.07±39.07	228.50±36.89	-0.962	0.340
Ferritin (ng/ml)	1369.63±645.88	651.03±417.00	5.120	<0.001**
TSAT%	30.08±10.85	32.55±20.97	-0.571	0.570

t- Independent sample t-test;
*p-value <0.05 S; **p-value <0.001HS; p-value >0.05 NS

Table 8 shows statistically significant difference between groups according to K and Ferritin.

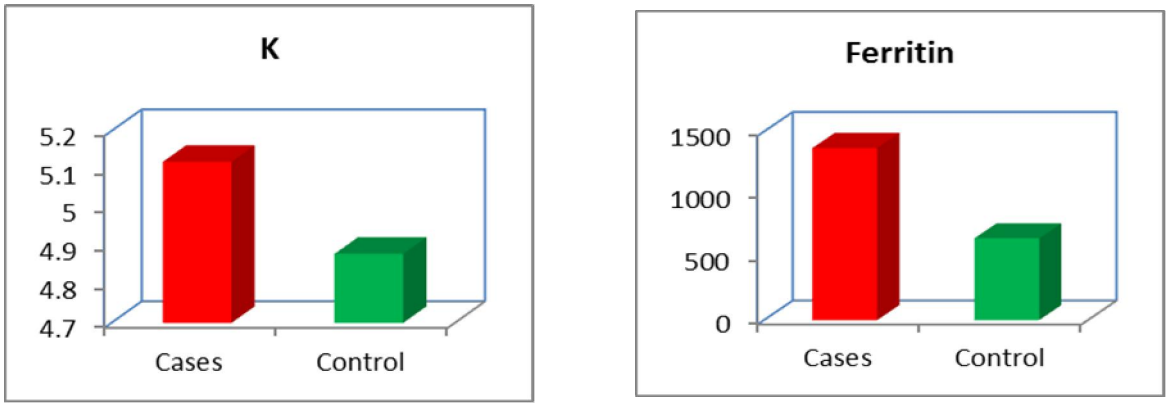

Fig. (4): Bar chart between groups according to K and Ferrtin.

Table (9): Correlation between post dialysis ET-1 with all parameters in cases group:

Cases	Post dialysis ET-1	
	r	p-value
Age (years)	-0.154	0.418
Duration of Dialysis (months)	0.371	0.044*
Na (mmol/l)	-0.153	0.420
K (mmol/l)	-0.239	0.203
Hb (g/dl)	0.146	0.442
Urea reduction ratio%	0.138	0.468
Ca (mg/dl)	-0.355	0.038*
Po4(mg/dl)	-0.183	0.334
PTH (pg/ml)	0.008	0.967
S. Iron (mcg/dl)	-0.130	0.493
TIBC (mcg/dl)	0.080	0.673
Ferrtin (ng/ml)	0.099	0.603
TSAT%	-0.282	0.131
Systolic blood pressure after Carvedilol (mmHg)	0.049	0.796
Diastolic blood pressure after Carvedilol (mmHg)	0.000	0.999
IDWG kg	-0.333	0.032*
UF rate (ml/kg/hr)	0.178	0.348
Dry weight (kg)	-0.389	0.034*
BMI (kg/m2)	-0.336	0.041*
Body surface area (m2)	-0.420	0.021*
Dose of Carvedilol (mg)	-0.059	0.758

rs: Spearman's rank correlation coefficient (rs)
*p-value <0.05 S; p-value >0.05 NS

Table 9 shows Positive correlation and significant between post dialysis ET-1 and duration of dialysis, while post dialysis ET-1shows negative correlation with Ca, IDWG kg, Dry weight, BMI and Body surface area (m2).

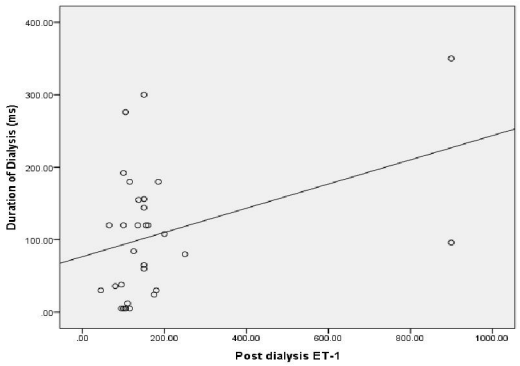

Fig. (5): Scatter plot, between post dialysis ET-1 and duration of dialysis in cases group.

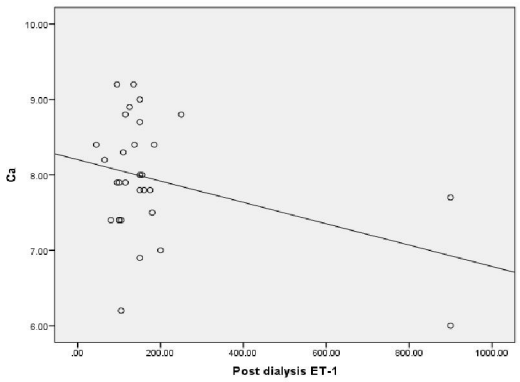

Fig. (6): Scatter plot, between post dialysis ET-1 and Ca in cases group.

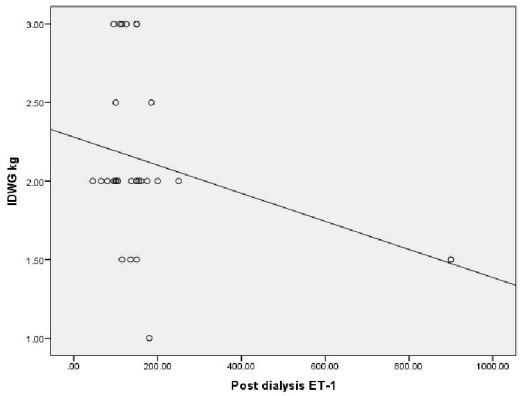

Fig. (7): Scatter plot, between post dialysis ET-1 and IDWG kg in cases group.

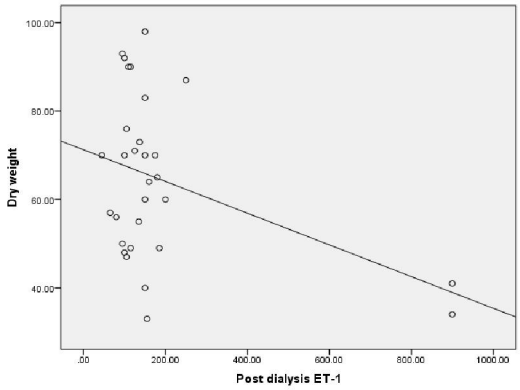

Fig. (8): Scatter plot, between post dialysis ET-1 and dry weight in cases group.

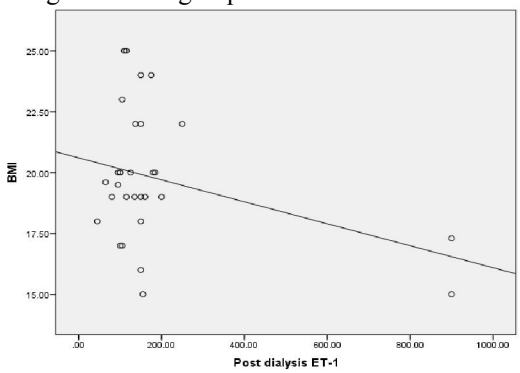

Fig. (9): Scatter plot, between post dialysis ET-1 and BMI in cases group.

Table (10): Correlation between delta ET-1 and IDWG in Cases group:

Cases	Delta ET-1(pre dialysis ET-1 –post dialysis ET-1) /pre dialysis ET-1	
	r	p-value
IDWG (kg)	0.353	0.056

rs: Spearman's rank correlation coefficient (rs)
*p-value <0.05 S; p-value >0.05 NS

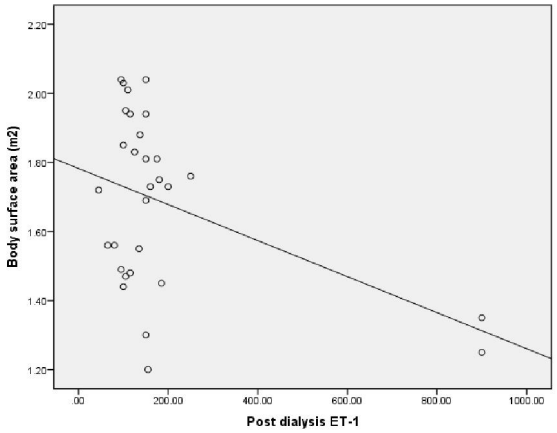

Fig. (10): Scatter plot, between post dialysis ET-1 and body surface area in cases group.

Table 10 shows Positive correlation and significant between IDWG and rate of rise of delta ET-1.

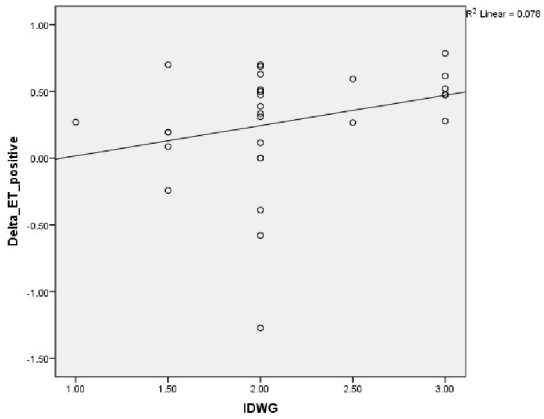

Fig. (11): Scatter plot, between IDWG and delta E-1 in cases group.

4. Discussion

Endothelial cell dysfunction is prevalent in intradialytic hypertension patients; ET-1 is the specific mediator of the intradialytic BP surge. Management of intradialytic hypertension patients should include an initial reassessment of dry weight. Patients with persistent intradialytic hypertension should be managed with less dialyzable drugs, and there is some evidence that carvedilol may provide a specific benefit. Modification of the dialysate sodium can be considered, although labs and hemodynamics should be carefully monitored [(2)].

Aim of our present work is to study the possible pathogenic role of E-1 in intradialytic hypertension

and the role of carvedilol in disease improvement in maintance hemodialysis patients.

The increase in SBP during hemodialysis was closely related to the increase in mortality, and SBP is increased in about 10–15% of patients after dialysis, according to some studies. Only one Indian study showed incidence of 49% in 100 patients studied have IDH. Previous studies have also shown that SBP increase during hemodialysis is a sign of poor prognosis in the short term [8].

Teng et al. [6] reported that, during HD there are usually two physical processes occurring, diffusion and ultrafiltration, which result in a reduction in circulating plasma volume. To maintain adequate blood pressure, the usual response is an increase in cardiac output and peripheral vascular resistance. The primary mechanism is the acute stimulation of the sympathetic nervous system, with an increase in stroke volume and heart rate, and vasoconstriction with an increase in peripheral vascular resistance.

The present study shows high level of endothelin-1 post dialysis in cases than control but not statistically significant. This result in agreement with other study ***Teng et al.*** [6] which comparing patients with intradialytic increases of BP to patients without IDH, hypertensive-prone patients exhibited an increase in systemic vascular resistance and a significant decrease in nitric oxide relative to endothelin-1 at the end of dialysis. Thus, the NO/ET-1 balance was significantly depressed in IDH compared the other patients, which may be the cause of the inappropriate elevation of peripheral vascular resistance. In a smaller study by ***Treweeke et al.*** [9] on nine patients with intradialytic increases in mean arterial BP, endothelin-1 significantly increased during HD. and, these study suggested that intradialytic hypertension mediated by an imbalance in important endothelial-derived vasoregulators.

During HD, in response to mechanical and hormonal stimuli, endothelial cells synthesize and release humoral factors, including the endothelial-derived relaxing factor, NO, and the vasoconstrictive factor, ET-I. It has been shown that the NO and ET-I balance is involved in the pathogenesis of intradialytic hypertension [9]. This is consistent with our current work.

The results of the present study are in agreement with ***Assimon et al.*** [10], who reported that, maintenance HD patients with intradialytic hypertension have abnormal in vivo endothelial cell function. They observed a 50% difference in the number of endothelial progenitor cells in those with intradialytic hypertension as compared to other HD patients without IDH. In addition, there was impaired endothelial-dependent vasodilation among those with intradialytic hypertension. In addition, ***Abramoff et al.*** [11] reported that ET-1 plasma levels have been found to be higher in HD hypertensive patients compared to other HD normotensive subjects.

The present study found statistically significance decrease in endothelin-1 in group A (cases) after dialysis then before it after Carvedilol intake. This mean that carvidilol has a role in E-1 decrease and disease improvement. This consistent with other studies ***Osama et al.*** [16] which found statistically significant increase of endothelin 1 in group A (cases) in comparison to group B (controls) before and after dialysis. In addition, in ***Osama et al.*** [16] there was statistically significant increase in endothelin-1 after dialysis in comparison to their values before dialysis in groups A & B. On the other hand, there was statistically significant decrease of NO in group A in comparison to group B before and after dialysis. There are discordant data about the ET-1 levels in HD patients since it has been reported to be unchanged ***Boesen*** [25] while ***Sheen et al.*** [26] reported that there is increase in ET-1 in HD patients, but ***Odetti et al.*** [27] reported that there is decreased in ET-1 in HD patients post-dialysis. Furthermore, it was reported that ET-1 levels vary according to type of membrane used during HD and UF rate [2].

Our results are in agreement with ***Safa et al.*** [28] who demonstrated increased plasma ET-1 levels in hypertensive ESRD patients during HD possibly stimulated by volume depletion with sympathetic activation, which may attenuate hypertensive HD effects, thus contributing to intradialytic and interdialytic hypertension.

Carvedilol is one such β-blocker with "low-dialyzability." It is the only β- blocker with evidence to reduce mortality rate in HD patients with dilated cardiomyopathy [12]. With these results, it can be a reasonable option to administrate potent β-blockers for HD patients to control BP.

Other study ***Takayasu et al.*** [13] demonstrated that the L/N-type calcium channel blocker, cilnidipine, failed to attenuate the increase in the SBP that occurred during HD in patients with intradialytic-HTN and no fluid overload. Cilinidipine decreased both the pre- and post-HD SBP, with a greater reduction in the latter. Furthermore, cilnidipine for 12 weeks exhibited no increase in the plasma norepinephrine or epinephrine levels after the HD.

Our current study shows significant relationship was found between IDH and cause of hemodialysis, previous HTN or other causes in CKD patients this in disagreement with other study which shows no relationship between incidence of IDH and previous hypertension, diabetes and other causes [1]. Although, no study examined the burden of IDH in known hypertensive patients, removal of anti-hypertensive medications during hemodialysis is one of the

proposed mechanisms for IDH [1]. No comparable data regarding the relationship of diabetes mellitus and IDH was found in previous studies.

Our current study shows statistically significance between both groups and anti-hypertensive medications that were taken by patients, which consistent with ***Karaboyas et al.*** [14] analysis of a large international HD cohort study, prescription of RAASi was 39% overall and varied by length of time on HD, and diabetes status, but varied minimally by history of CHF or CAD. RAASi prescription was associated with an 11% lower all-cause mortality rate among incident HD patients and a 6% lower mortality rate among prevalent HD patients, with no evidence of interaction with diabetes, CAD, or CHF. Inverse associations with mortality were also observed for BB and CCB, and appeared stronger for ARB than ACEi.

ACEi were more frequently used by intradialytic-HTN subjects who took more antihypertensives in general. It is uncertain whether this is an indication bias or whether the fact that lisinopril and quinapril are dialyzable contributed to the increased incidence of intradialytic hypertension in the case group [15]. This is not consistent with our study which shows improvemenent of intra dialytic hypertension with carvedilol in cases group.

Combination of amlodipine with beta-adrenoceptor blocker provided adequate control of blood pressure in all phases of dialysis with least intra-dialysis complication [16].

Intradialytic hypertension can occurs caused by activation of the RAAS. Ultrafiltrasion during HD make decreased of intravasculer volume, and then activated RAAS and increased of renin and angiotensin II secretion. This condition can causing a sudden rise in systemic vascular resistance and an increase in blood pressure [17].

Hypervolemia is supposed to be the most common factor. In the presence of intradialytic hypertension, an increase in ultrafiltration rate and reduction of dry weight were the usual strategies that had been adopted and were suggested to be effective. However, most patients present with even higher blood pressure during HD after increases in ultrafiltration rates. Factors other than hypervolemia must participate in the pathogenesis of acute increase of blood pressure during HD. If hypervolemia did not exist, is it possible that the faster refilling rate of plasma in hypertension-prone HD patients is initiated by the inappropriate elevation of PVR and the arteriolar vasoconstriction results in decreased mean intracapillary hydraulic pressure that favors refilling of the plasma volume [18].

Intradialytic hypertension is often attributed to volume overload. In a cross-sectional study, ***Nongnuch et al.*** [1] reported that patients who experienced a pre- to post-dialysis systolic BP rise (vs. not) had higher pre- and post-dialysis extracellular water to total body water ratios and lower ultrafiltration volumes. Additionally, intensification of ultrafiltration has been shown to improve BP, ejection fraction and cardiac output among individuals with intradialytic hypertension [11] provide further support for a link between volume status and intradialytic hypertension. We found that patients who experienced more frequent intradialytic hypertension had an incrementally higher hazard of 30-day volume-related hospitalizations.

Although inappropriate elevations of PVR seemed reasonable to explain the faster refilling of plasma volume, the possibility of some of these hypertension-prone HD patients also having subclinic hypervolemia still cannot be excluded. In fact, it has been proposed that the susceptibility to hypervolemia is increased in the renal patients due to inappropriately elevated activity of pressor systems (and/or decreased activity of depressor systems), including abnormalities of ET-1 and NO [18]. In addition to the factors mentioned above, disequilibrium syndrome, hypokalemia, hypercalcemia, increased Hct due to ultrafiltration, or removal of antihypertensive medications have also been proposed to be responsible for intradialytic hypertension. This is in agreement with our current study which shows statistically significant difference between groups according to K and Ferritin.

In the present study statistically significant difference between groups according to Ferritin, this was consistent with ***Teng et al.*** [6] which showed significant increase in hematocrit after dialysis in comparison to values before dialysis in groups A & B.

Our current study shows negative correlation with post dialysis endothelin-1 and Ca in cases group. As regard serum calcium before dialysis, it ranged from 6 to 9.2 with a mean of 7.9±0.8. These results are in contradiction to ***Teng et al.*** [6]. Who reported that, there was statistically significant increase of calcium in IDH and proposed that, it may work a minimal part in Pathophysiology of IDH. The possible explanation may be attributed to dialysate buffer.

Our current results shows negative correlation with post dialysis endothelin-1 and IDWG, Dry weight, BMI and Body surface area (m2) indicate that intradialytic hypertension may be a risk marker for impending adverse events secondary to volume overload and suggest that prompt volume assessment among hemodialysis patients who experience frequent episodes of intradialytic hypertension is warranted. In fact, challenging prescribed target (estimated “dry”) weight via increased ultrafiltration has been shown to improve intradialytic hypertension [19].

The percentage of interdialytic weight gain (overall weight gain/estimated dry weight x 100) predicts increased pre-HD systolic blood pressure and greater reduction in systolic blood pressure from pre- to post-HD, particularly in non-diabetics, younger patients, and those with greater estimated dry weight. In one large, observational study, increased interdialytic weight gain (IDWG) was associated with increased mortality [(20)].

Moreover, the exact pathophysiology of blood pressure fluctuations during hemodialysis has not been identified in this study, and the impact of various factors (e.g. ultrafiltration method) on patients' blood pressure fluctuations were unknown.

In this study, no relation was found between the incidence of IDH and the age and sex of the patient. No previous studies demonstrated a statistically significant difference among males and females. According to a study by ***Inrig et al.*** [(20)] on 32,295 patients, incidence of IDH was found more amongst the elderly. Similarly, in our study we found that IDH occurred more frequently in the elderly but it was not statistically significant.

In search for clinical and laboratory characteristics associated with volume status, (edema, lower BMI, higher SBP). None of these parameters displayed both a good sensitivity and specificity. A previous study reported that pedal edema correlates well with cardiovascular risk factors and left ventricular mass, but it did not reflect volume in HD patients as assessed by cardiac biomarkers and echocardiography [(21)]. Our study shows no statistically significance difference between groups according to BMI, UF rate, Dry weight, Body surface area and inter dialytic weight gain.

Silva et al. [(22)] found that higher dialysate bicarbonate concentration was associated with lower post-dialysis cardiac index and BP, while higher dialysate to serum potassium gradient was associated with more preserved BP and cardiac index. Those discordant results between previous reports and ours are likely from differences in study design and population.

In this present study we found negative correlation and significance between post dialysis ET-1 with Na and K in Control group. It is studied in literature that there is an association between dialysate to serum sodium gradients and BP increase during dialysis in patients with IDH, although it is unclear if this is related to endothelial cell activity or acute osmolar changes. In addition to probing the dry weight of patients with intradialytic hypertension, other management strategies include lowering dialysate sodium and changing anti-hypertensives to include carvedilol or other poorly dialyzed anti-hypertensives will help to reduce IDH [(2)]. All patients in our study were prescribed similar dialysis prescription to remove this confounding factor, and all patients of IDH were prescribed non-dialyzable anti-hypertensives for treatment of IDH. Except angiotensin receptor blocker (ARB) and angiotensin-converting enzyme (ACE) inhibitors, most of other drugs are dialyzed and hence incidence of IDH is more when more drugs are prescribed.

The primary goal in management of intradialytic hypertension is to address the likely underlying etiology and reduce the patient's overall risk for longer term cardiovascular morbidity and mortality. Many patients with intradialytic hypertension may not appear overtly volume overloaded as they are older, smaller and have smaller interdialytic weight gains. Because of the strong association between extracellular volume overload and intradialytic hypertension from observational studies, dry weight reduction should be a primary consideration in the initial management. Modification of dialysate sodium is another option in patients with intradialytic hypertension. In general hypertensive hemodialysis patients, decreasing dialysate sodium concentration reduces interdialytic thirst and weight gain. In one randomized crossover study of patients with recurrent intradialytic hypertension, BP decreased during treatments with low dialysate sodium (serum sodium minus 5) and increased during treatments with high dialysate sodium (serum sodium + 5) [(23)]. It remains unclear how effectively this intervention lowers ambulatory BP or overall mortality risk in patients with intradialytic hypertension with some epidemiologic data from large dialysis cohorts suggesting an association between lower dialysate sodium and increased mortality among patients with lower serum sodium levels.

Physical examination has proven to be fairly unreliable in identifying volume overload compared to other methods. In the clinical research setting, multifrequency bioimpedance spectroscopy has emerged as a potential tool to improve the assessment of extracellular volume. Several pilot studies have shown the ability to safely reduce volume overload or lower BP [(24)] but there are numerous limitations to the use of this equipment for widespread use in clinical practice related to cost, availability, and patient exclusion criteria. As highlighted above, high postdialysis BP likely identifies the presence of chronic extracellular volume overload compared to predialysis BP and may be most useful for evaluating volume status in the absence of bioimpedance. In patients with recurrent intradialytic hypertension, one uncontrolled pilot study showed some benefits of administering carvedilol [(2)]. In these patients, there was lower ambulatory BP, improved endothelial cell dysfunction and reduction in the incidence of

intradialytic hypertension after 8 weeks of carvedilol therapy.

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