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Impact of Hemodialysis Time Prolongation on Blood Pressure Control

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Abstract

Introduction**:** Hypertension prevalence among end-stage renal disease (ESRD) patients range from 76% to 90%. Increasing the duration of dialysis time, either by longer session hours or increased sessions, aiming at reducing the dry weight to achieve euvolemia, may be beneficial for individuals who failed to achieve target BP or ideal volume status during standard HD prescription hours.

Objective: We aimed to study the effect of increasing hemodialysis session time on blood pressure control.

Methods: This observational study was conducted on 50 hypertensive prevalent HD patients on thrice-weekly maintenance HD. Patients were divided into 2 groups: (A) 25 patients who received longer hemodialysis session (4.5 hours) and (B) 25 patients HD who received the usual 4 hours session. They were followed up for a period of 6 months to assess changes of pre-dialysis blood pressure to monitor response.

Results: Ultrafiltration volume declined significantly with longer HD sessions compared to conventional sessions (p-value < 0.001 versus 0.523). Longer HD session time group was associated with highly significant decline in mean SBP, (p-value < 0.001). Moreover, longer HD session time group was associated with highly statistically significant decline in mean DBP, (p-value < 0.001). The decline in mean perdialysis SBP & DBP was -17.27 & -9 mmHg respectively and the rate of decline of postdialysis SBP & DBP was -6.45 & -12.38 mmHg respectively at 6th month compared to values in 1st month of follow up period.

Conclusion: Longer HD session duration is associated with better improvement in UF volume, mean SBP & DBP, pre-dialysis SBP & DBP and post-dialysis SBP & DBP as well.

Keywords: Hemodialysis, Hypertension, ESRD.

INTRODUCTION

Hypertension represents a leading cause of end-stage renal disease and a well-recognized risk factor for cardiovascular in ESRD patients on regular dialysis. The lack of a strict definition for diagnosing hypertension (HTN) as well as exact technique of blood pressure (BP) measurement and monitoring leads to the variable prevalence of hypertension in ESRD ranging from 76% to 90% [(1)]. Despite this high prevalence of HTN, owing to the complex pathophysiology of HTN in HD, it is inadequately controlled among most of this population. Many causes are implicated in the mechanism of HTN such as sodium and volume overload, increased arterial stiffness, over activation of the sympathetic nervous system, activation of renin-angiotensin-aldosterone system, endothelial dysfunction, high prevalence of sleep apnea and use of recombinant erythropoietin therapy [(2)]. As the ability of hemodialysis (HD) patients to regulate sodium and water homeostasis is severely impaired, sodium retention and volume overload are among the main etiologies for underlying HTN development and thus, non-pharmacologic strategies are fundamental to achieve BP control in these patients [(3)].

Current strategies to manage volume overload include both dietary and dialytic approaches [(4)]. These treatment interventions aim to reduce the target dry weight to achieve euvolemia. This target dry weight reduction can make hypertension control easier or even normalize BP in the great majority of dialysis patients [(5)]. Increasing the duration of dialysis time, either by longer session hours or increased sessions frequency may be beneficial for individuals who failed to achieve target BP or ideal volume status during standard HD prescription hours [(6)].

BP tends to climb during the interdialytic period, together with interdialytic weight gain [(7)]. Extended HD includes reduction in the duration between sessions that leads to a reduction in the amount of interdialytic fluid accumulation [(8)].

Conventional HD is frequently associated with elevated ultrafiltration rate (UFR) with its consequences like increased risk of muscle cramps and hypotensive episodes with subsequent saline infusion with its adverse effect on ECV [(9)]. It is proposed that it is better to put a maximum UFR required to achieve the desired fluid removal and vary the duration of the treatment to achieve that target volume to avoid the effects of UF on systemic hemodynamics [(10)]. There is a rational to adopt extended dialysis time approach that is defined as any schedule with increased hours per session or increased sessions per

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week. It is valuable to note that the popularity of thrice-weekly HD is not based on the superiority of clinical outcomes but emerged as a consequence of a triad of technology advancement, financial burden and post hoc analysis of the National Cooperative Dialysis Study [11].

It is also necessary to individualize BP treatment plans to incorporate other co-morbidities in patients undergoing hemodialysis. All classes of antihypertensives may be used, although conclusive data are limited [12]. It is recommended to use antihypertensive drugs for patients in whom BP cannot be controlled appropriately by non-pharmacological measures, as this is associated with improvement in mortality. When prescribing a drug to patients on dialysis, the characteristics of each drug, including its dialyzability, should be considered [13].

This study aimed to assess such a relation between the effect of increasing hemodialysis session time on blood pressure control among this population.

PATIENTS AND METHODS

This observational study was conducted on 50 end stage renal disease patients on thrice-weekly maintenance HD at dialysis units of Ain Shams University Hospitals.

Ethical approval:

This study was performed in accordance with the ethical standards of Ain Shams University Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics committees reference number: 00017585. A written informed consents were obtained from all participants included in the study.

All patients were older than 18 years, clinically stable hypertensive patients according to KDOQI definition of hypertension as pre-dialysis BP more than 140/90 mmHg and/or post dialysis more than130/80 mmHg [14].

Patients with endocrinal causes of hypertension and Patients with decompensated medical conditions were excluded from our study.

All patients were dialyzed with 1.8–2.2 m^2 high flux synthetic (Helixon ®) membranes with blood flow rate of 300 ml/min. Bicarbonate dialysate solution with dialysate flow rate of 500ml/ min was instituted. Dialysate fluid composition after dilution (dilution ratio 1: 34) was : sodium 106 mmol/l (before addition of sodium bicarbonate), potassium 2 mmol/l, calcium 1.5 mmol/l, mesangium 0.50 mmol/l, bicarbonate 33 mmol/l, chloride 111 mmol/l and sodium after addition of NaHCO3 140 mmol/l.

Patients were divided into 2 groups: longer HD session group (A) included 25 ESRD, hypertensive patients on thrice-weekly regular HD who received longer session hemodialysis session; each session was 4.5 hour. Conventional HD session group (B) includes 25 ESRD, hypertensive patients on thrice-weekly regular HD who received the usual 4 hour session. All the patients in both groups were subjected to full history taking including the etiology of kidney disease and duration of hemodialysis with the type of vascular access as well thoroughly physical examination.

Patients' drug intake during follow up period was recorded including calcium containing or non-calcium containing phosphate binders and active vitamin D replacement, blood transfusion procedures during the study were followed and recorded.

Revision of antihypertensive medications for all participants was done, and drug classes prescribed on individual basis according to the patients' co-morbid conditions. Dosage was adjusted to achieve BP < 140/90 mmHg.

All patients are laboratory investigated on monthly basis for urea reduction ratio (URR) that was calculated as: (predialysis urea- postdialysis urea / predialysis urea) x 100 [14], and for complete blood count, CBC to avoid unnecessary overuse of ESAs, as well as serum calcium (Ca), phosphorus (PO_4) and their product (Ca-p). Patients were instructed to restrict their salt intake as much as possible and followed to ensure optimal dialysis prescription through reduction of dialysate Na to 135mmol/L. Dry weight of the patient was reassessed regularly to ensure proper control of the blood pressure and to ensure close adherence to HD treatment through avoidance of post dialytic fatigue and hypotension with subsequent missed sessions.

Our participants were closely followed for dialysis dose: group 1 received total of 4.5 hours per session while group 2 received the usual 4 hours schedule [15]. Then,Patients were observed for a period of six months for changes of pre-dialysis blood pressure to monitor response.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. The following tests were done: Independent-samples t-test of significance was used when comparing between two means. Paired sample t-test of significance was used when comparing between related samples. Chi-square (x^2) test of significance was used in order to compare proportions between qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was

considered significant as the following: Probability (P-value), P-value ≤ 0.05 was considered significant. P-value < 0.001 was considered as highly significant. P-value > 0.05 was considered insignificant.

RESULTS

This is observational six-month follow up study that involved 50 hypertensive, hemodialysis patients randomized into two groups, longer HD session group (A) and conventional HD group (B), each comprising 25 patients. There was no statistically significant difference between groups as regard demographic data including age, sex and duration of HD, vascular access, hepatitis C virus status and post dialysis body weight. Both groups were age matched with mean age of 51.16 ± 10.60 & 51.12 ± 11.52 years for group A & B, respectively (p-value 0.499), with male predominance representing 64% in group A and 56% in group B, (p-value 0.564). Mean duration since patients initiated their maintenance sessions is 4.52 ± 2.16 & 5.44 ± 2.74 years for group A & B, respectively, (p-value 0.194). AVF was the most predominant vascular access representing 68% and 92% in group A & B, respectively, (p-value 0.179) as shown in table (1).

Table (1): Comparison between groups as regards demographic data.

Demographic data	Study group (A) *(n=25)*	Control group (B) *(n=25)*	t/x2#	p-value
Age (years) Mean ± SD Range	 51.16 ± 10.60 25.00-64.00	 51.12 ± 11.52 30.00-64.00	0.633	0.499
Sex Male Female	 16 (64.0%) 9 (36.0%)	 14 (56.0%) 11 (44.0%)	0.333#	0.564
Duration of HD (years)				
Mean ± SD	4.52 ± 2.16	5.44 ± 2.74	1.737	0.194
Range	1.00-8.00	1.00-10.00		
Vascular Acess				
Central Venous Catheter	2 (8.0%)	0 (0.0%)	4.900#	0.179
Fistula	17 (68.0%)	23 (92.0%)		
AVG	3 (12.0%)	1 (4.0%)		
Permicath	3 (12.0%)	1 (4.0%)		
HCV status				
PCR negative, antibody +ve	5 (20.0%)	4 (16.0%)	0.159#	0.924
Negative IgG	10 (40.0%)	10 (40.0%)		
Positive IgG	10 (40.0%)	11 (44.0%)		
Postdialysis body weight (kg)				
Mean ± SD	80.23 ± 15.21	79.93 ± 16.15	0.005	0.946
Range	57.95-105.37	51.64-103.46		

Regarding the etiology of ESRD, there was no statistically significant difference between groups and HTN was the commonest cause representing 48% &40% in group A & b, respectively (Table 2).

Table (2): Comparison between groups as regard etiology of ESRD

Etiology of ESRD	Study(A) group *(n=25)*	Control(B) group *(n=25)*	t/x2#	p-value
Unknown	10 (40.0%)	9 (36.0%)	8.893#	0.180
D.M	2 (8.0%)	3 (12.0%)		
HTN	12 (48.0%)	10 (40.0%)		
HTN&DM	1 (4.0%)	2 (8.0%)		
Gestational HTN	0 (0.0%)	1 (4.0%)		

No statistically significant difference is observed between groups as regards urea reduction ratio, (p-value 0.123) (Figure 1) and other laboratory investigations including hemoglobin (0.959), white blood cell count (p-value 0.295), platelets count (0.779) and calcium – phosphate product (p-value 0.676) (Table 3). However, there was statistically significant

difference between groups as regards serum phosphate level at 2nd month of follow up period, (p-value 0.003) as shown in figure (2).

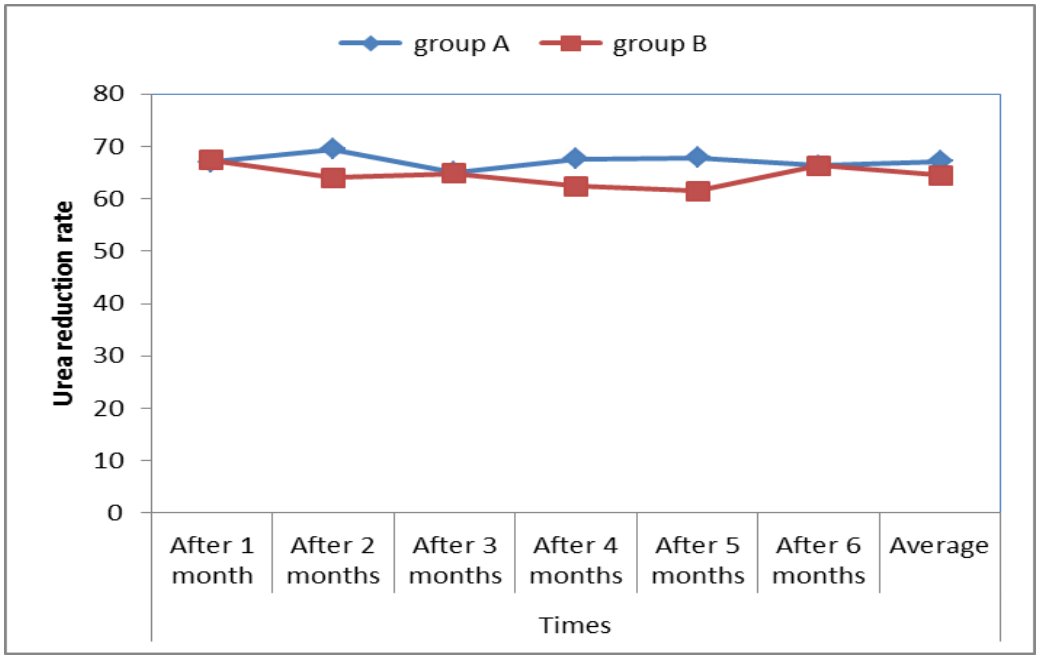

Figure (1): Comparison between groups as regard urea reduction ratio

Table (3): Comparison between groups as regards average laboratory results over the study period

Lab results	Group A *(n=25)*	Group B *(n=25)*	t-test	p-value
Calcium phosphate product				
Mean ± SD	58.23 ± 9.19	59.64 ± 13.89	0.177	0.676
Range				
Hemoglobin (HBG) (gm/dl)				
Mean ± SD	10.14 ± 1.41	10.12 ± 1.96	0.003	0.959
Range	7.63-12.73	6.63-14.92		
White blood cells (WBCs)				
Mean ± SD	6.42 ± 1.74	5.87 ± 1.94	1.123	0.295
Range	3.97-11.08	0.83-9.27		
Platelets (PLT)				
Mean ± SD	241.86 ± 7.22	236.69 ± 5.41	0.079	0.779

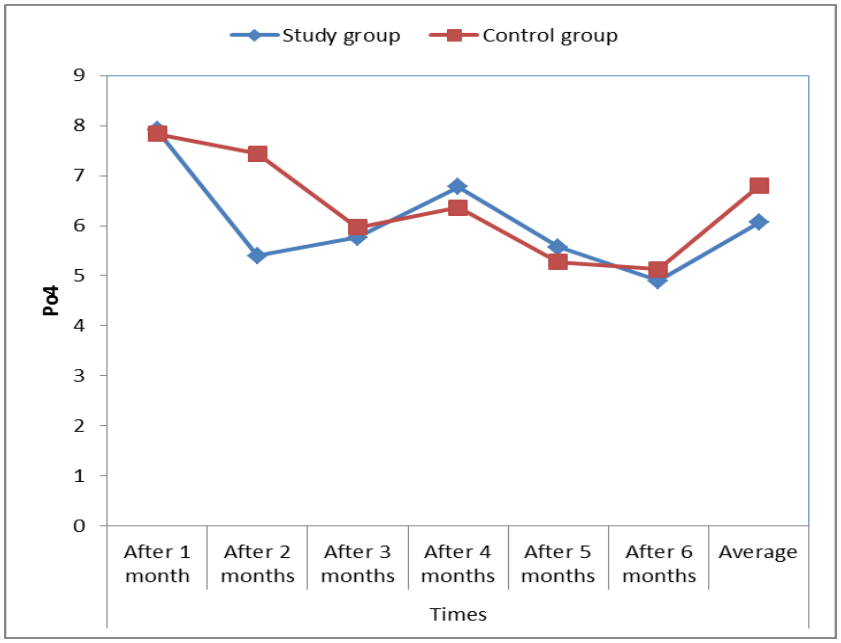

Figure (2): Comparison between study group and control group as regards serum phosphate level

Regarding ultrafiltration volume, there was statistically significant decline associated with longer HD session in group A patients (p-value < 0.001) compared to non-significant decline in group B who received conventional HD session time, (p-value 0.523) as shown in table (4**).**

Table (4): Comparison between groups as regard UF volume

UF volume	group A *(n=25)*	group B *(n=25)*	t-test	p-value
After 1 month				
Mean ± SD	3.72 ± 0.68	3.34 ± 0.89	2.895	0.095
Range	2.15-5.23	1.77-5.00		
After 6 months				
Mean ± SD	2.96 ± 0.95	3.00 ± 2.73	0.005	0.945
Range	1.38-5.62	-6.54-11.62		
Mean difference	-0.76	-0.34		
Paired sample t-test	4.279	0.643		
p-value	<0.001**	0.523		

Longer HD session time session was associated with highly significant decline in mean SBP, (p-value < 0.001). The mean difference was significantly higher at 1st month compared to 6th month (p-value 0.046) (Table 5).

Table (5): The effect of longer HD session time on SBP (mmHg)

SBP (mmHg)	Group A (n=25)		Paired Sample t-test		
	Predialysis *(n=25)*	*Postdialysis (n=25)*	Mean difference	t-test	p-value
After 1 month	158.39±12.70	142.47±12.14	-15.92±11.06	7.192	<0.001**
After 6 months	141.12±4.52	130.09±6.77	-11.02±6.73	8.201	<0.001**
Mean difference	-17.27	-12.38	4.9	2.683	0.024*
Paired sample t-test	4.531	4.453	1.892		
p-value	<0.001**	<0.001**	0.046*		

As regards mean difference in SBP, it was significantly higher in longer HD session group (A) compared to conventional HD session time (B) at 1st month of follow up, (p-value 0.025) (Table 6).

Table (6): Comparison between groups as regards the effect of HD session on SBP (mmHg)

Mean difference in SBP(mmHg)	Group A *(n=25)*	Group B *(n=25)*	t-test	p-value
After 1 month				
Mean ± SD	-15.92 ± 11.06-	-9.70 ± 7.55	5.375	0.025*
Range	-43.80_6.90	-30.00_5.40		
After 6 months				
Mean ± SD	-11.02 ± 6.73	-8.84 ± 11.03	0.712	0.403
Range	-20.00_4.90	-52.00_4.60		
Mean difference	4.9	0.86		
Paired sample t-test	1.826	-3.91		
p-value	0.080	0.699		

As regards mean DBP in group A, highly statistically significant reduction was noted after HD session compared to predialysis values at 1st month and 6th month period interval (p-value < 0.001). The comparison of degree of decline between1st & 6th month was insignificantly higher at 1st month (P-value 0.139). Predialysis DBP showed highly significant reduction after 6 month of follow up period (P-value < 0.001). As regards postdialysis DBP, statistically significant decline after 6th month was detected (p-value0.009) (Table 7).

Table (7): The effect of longer HD session time on DBP (mmHg)

Diastolic Blood Pressure (mmHg)	Group A (n=25)		Paired Sample t-test		
	Predialysis *(n=25)*	Postdialysis *(n=25)*	Mean difference	t-test	p-value
After 1 month	96.28 ± 5.62	87.56 ± 8.15	-8.72 ± 7.05	6.189	<0.001**
After 6 months	87.28 ± 4.02	81.11 ± 4.09	-6.17 ± 4.74	6.513	<0.001**
Mean difference	-9	-6.45	2.55	1.803	0.078
Paired sample t-test	6.513	3.537	1.501		
p-value	<0.001**	0.009*	0.139		

Table (8) showed that longer HD session time session was associated with highly statistically significant decline in mean DBP compared to conventional hemodialysis group (B) (p-value < 0.001 at 1st month and p-value 0.002 at 6th month).

Table (8): Comparison between groups as regard mean difference in DBP (mmHg)

Mean difference in DBP (mmHg)	Group A *(n=25)*	Group B *(n=25)*	t-test	p-value
After 1 month				
Mean ± SD	-8.72 ± 7.05	-2.71 ± 5.37	11.481	<0.001**
Range	-18.50_8.50	-15.40_4.60		
After 6 months				
Mean ± SD	-6.17 ± 4.74	-2.18 ± 3.71	7.984	0.002*
Range	-13.80_2.50	-13.10_4.60		
Mean difference	2.55	0.53		
Paired sample t-test	-1.400	-0.455		
p-value	0.174	0.653		

DISCUSSION

In our study, we found statistically highly significant positive correlations between prolonged HD session time and blood pressure control, (p-value < 0.001). Similarly, another study by **Bucharles and his Colleagues** [9] assumed that longer HD session is associated with reduction in ultrafiltration rate that, agrees with our results and he noticed improvement in left ventricular hypertrophy and cardiac function with reduction in blood pressure**.** Clinicians thought that increasing the time of dialysis session might represent an additional approach to control blood pressure among HD patients who remain hypertensive despite intensification of volume removal [16]. Longer session duration may be beneficial as it leads to improve tolerability of the treatment mainly due to slower ultrafiltration rate and greater removal of uremic toxin particularly middle molecules, these lead to improvement in cardiovascular

morbidity and mortality [17]. This can be explained by smaller plasma dialysate electrolyte gradient with less dramatic volume shift and less sympathetic hyperactivity [15]. Thus longer HD provides more time for equilibration between intracellular compartments and extracellular spaces during fluid removal with subsequent lower activation of renin- angiotensin- aldosterone system and reduction in catecholamines release, this decrease shear stress on vascular walls [8].

Our study showed statistically highly significant reduction in mean SBP associated with longer HD session, (p-value < 0.001). The mean difference in SBP was higher with longer HD session (-15.92 ± 11.06 mmHg) compared to conventional HD time (-9.70 ± 7.55 mmHg) after 1st month of follow up period, (p-value 0.025).

Longer HD was associated with statistically highly significant decline in predialysis SBP at 6th month of follow up period, (p-value < 0.001), the rate of decline was higher with longer HD session time (-17.27 mmHg) compared to conventional session HD (-7.79 mmHg).

Longer HD was associated with statistically highly significant reduction in postdialysis SBP, (p-value<0.001), the rate of decline was higher in longer session receipt patients (-12.38 mmHg) than in those received the usual session time (-6.92mmHg). DOPPS study reported that longer HD was associated with lower pre- & postdialysis SBP levels and better achievement of clinical guidelines for BP control [15]. **Ayus and Colleagues**[18] prospective cohort study was associated with significant reduction in mean SBP with prolonged HD (short daily dialysis) after a period of 6 month of follow up that is thought to be related to significantly increased cumulative dialysis dose and ultrafiltration.

Our results showed association between longer dialysis session and statistically significant reduction in mean DBP, (p-value < 0.001), the degree of decline was (-8.72 ± 7.05 mmHg) and (-6.17 ± 4.74 mmHg) at 1st & 6th months of follow up period, respectively. However this rate was (-2.71 ± 5.37 mmHg, p-value 0.029) and (-2.18 ± 3.71 mmHg, p-value 0.007) with conventional dialysis group at the same period interval.

Longer HD regimen was associated with highly significant decline in predialysis DBP at 6th month of follow up, (p-value < 0.001). The rate of decline was also higher with longer HD regimen (-9 mmHg) compared to conventional regimen (-3.35 mmHg).

As regards postdialysis DBP, statistically significant decline was correlated to longer HD session, (p-value 0.009) compared to insignificant decline with the usual HD regimen.

Data analysis from randomized controlled trial of Frequent Hemodialysis Network (FHN) that randomized 245 patients to 12 month of frequent dialysis (6 times per week) versus conventional HD, showed significant reduction in predialysis SBP (-10 mmHg), postdialysis SBP (-8 mmHg), predialysis DBP (-5 mmHg), and postdialysis DBP (-3 mmHg) with (intensive) frequent regimen [19]. **Susantitaphong and Colleagues** [20] meta-analysis investigated the effect of intensive dialysis on cardiovascular parameters and reported significant reduction in both SBP (-14.1 mmHg) & DBP (-7.1 mmHg) that was associated with frequent (2 -8 hour > 3 per week) or extended HD (> 4 hours, thrice-weekly). Another recent study that was conducted on 40 adult prevalent hypertensive patients to study the effect of intensive HD (4 times per week; ≥ 16 hours per week) on LVH & BP control. They reported reduction in SBP, DBP and mean BP after 2 months of intensive HD compared to pre-intervention values, (p-value < 0.001) [21]. This comes in agreement with the result of 2 month of frequent daily dialysis (6 per week) that was associated with significant reduction of predialysis SBP (-7 mmHg) and DBP (-3.9mmHg) compared to thrice-weekly HD in FHN Trial [19].

Our results showed association between longer HD session and statistically significant decline in ultrafiltration volume at 6 months of follow up, (p-value < 0.001) compared to insignificant reduction in the usual dialysis group, (p-value 0.523). Similarly, marked reduction in UF volume at 6 & 12 months of extended (short daily) HD was reported in **Ayus and Colleagues** [18] prospective cohort study. It is thought that longer session provide less intensive HD, which significantly reduces thoracic fluid content representing better fluid removal with better hemodynamic stability. Thus, longer HD session may be more beneficial than conventional dialysis in improving patient tolerability and clinical outcomes [22].

Our results showed statistically significant decline in serum phosphate at 2 month of longer HD, (p-value < 0.001) compared to the usual hour regimen. However, another study reported that a significant reduction in serum phosphate level that was observed with extended dialysis (≥24 hour weekly) (p-value<0.0001) compared to conventional regimen (≤ 18 hour weekly), which was apparent at 3 month of study and maintained throughout the study (p-value 0.016) (23).

Our results showed negative correlation between longer HD sessions and patients' laboratory investigations including calcium-phosphate product, hemoglobin level, white blood cells count, and platelets concentration. However, data collected from DOPPS study reported better control of anemia; improvement in inflammatory status indicated by lower white blood cell count and improved phosphorus level with longer treatment time that may be attributed to better removal of small and large molecules [15].

Our results showed that increasing HD session time into 4.5 hours compared to the usual 4 hour session

was not associated with statistically significant improvement in URR%. This contradicts with another multi-center study that reported significant higher Kt/V in longer HD group patient compared to the usual session time group (p-value 0.032). This study was conducted on 50 hemodialysis patients divided into groups, group received the usual 4 hour session and the other group received prolonged HD session, (5hours) for 2 months [(22)].

CONCLUSION

Hypertension has high prevalence in hemodialysis patients mainly related to sodium and fluid overload. Adequate dialysis is efficient tool to remove excess sodium & water. Longer HD session duration is associated with better improvement in UF volume, mean SBP & DBP, pre-dialysis SBP & DBP and post-dialysis SBP & DBP as well. It is necessary to raise awareness about the benefits of longer and frequent HD.

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