Research Article

Control of Blood Pressure and Anti Hypertensive Drug Profile in End Stage Renal Disease Patients Undergoing Maintenances Hemodialysis: An Observation and a Retrospective Study

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ABSTRACT

Introduction: Hypertension is the second leading cause of End Stage Renal Disease after diabetes mellitus. If hypertension is an etiologically significant cardiovascular risk factor in hemodialysis patients, the first step would be to assess the level of BP accurately. To manage hypertension, limiting dietary fluide intake, and individualizing dialysate sodium delivery would be the initial steps as non pharmacological measures. Therefore as a pharmacological measurement, study was conducted to determine control of blood pressure by anti hypertensive drug treatment. **Material And Method:** Treatment and control of hypertension was assessed retrospectively in a cohort of 100 clinically stable, adult patients undergoing hemodialysis. Frequency and duration of hemodialysis were also assessed. For quality of life, kidney disease outcomes quality initiative-survey form™ 1.3 health survey was used for 40 adult patients undergoing hemodialysis. **Results:** Hypertension was documented in patients (n = 97) with complicated kidney disease (97.16%) and patients (n = 85) with non-complicated kidney disease (85.66%). Hypertension was adequately controlled in only 2.83% (n = 3) patients with complicated kidney disease and 14.33% patients (n = 15) with non complicated kidney disease undergoing maintainanace hemodialysis. Patients with non-diabetic kidney disease had better quality of life as compared to the patients with diabetic kidney disease. **Conclusion:** Control of hypertension, particularly systolic hypertension, in patients undergoing hemodialysis for prolong period was inadequate, despite recognition of its prevalence and the use of antihypertensive drugs. Optimizing the use of medications and closer attention to non pharmacological interventions, may improve control of BP.

Key words: Anti hypertensive drugs, Chronic kidney failure, End stage renal disease (ESRD), Hemodialysis, Hypertension, Quality of life.

INTRODUCTION

End-stage renal disease (ESRD) is the final stage of chronic kidney disease (CKD), known as stage-5 CKD, and is defined by a glomerular filtration rate (GFR) of less than 15 mL per minute per 1.73 m^2 body surface area and the need for renal replacement therapy, either dialysis or transplantation, to sustain life1. While the goal for patients with earlier stages of CKD is to delay progression of kidney disease to this final stage, many patients ultimately develop ESRD and must rely on chronic dialysis to maintain fluid and electrolyte control. Renal replacement therapies for patients with ESRD include chronic hemodialysis, peritoneal dialysis, and kidney transplantation.[1] ESRD can be caused by an acute irreversible insult to the kidney, a primary kidney disease, or a systemic illness. Diabetes mellitus continues to be the leading cause of ESRD. Hypertension is the second leading cause of ESRD, increased by almost 50%. Glo-

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merulonephritis, cystic kidney disease, and HIV-related nephropathy are among the other etiologies. Although the number of new cases of ESRD attributed to these other etiologies is less than from diabetes and hypertension, the total number of ESRD patients with these conditions as the primary cause of their kidney disease, prevalence of disease patients have increased in the past decade. This is due, in part, to the decrease in mortality among ESRD patients[1] Hypertension is second most the leading independent cause of end-stage renal disease (ESRD) after diabetes, the risk of which increases continuously with the extent and duration of elevated blood pressure (BP). In addition, a substantial number of patients with diabetes also have hypertension, which can accelerate the progression of nephropathy and the onset of ESRD. In general, chronic renal disease can be a cause or a consequence of hypertension, majority of the patients with chronic renal disease have hypertension and without anti-hypertensive intervention, this can result in a vicious cycle of worsening renal function. ESRD has a negative impact on the prognosis of patients in terms of survival and quality of life, it is also associated with substantial economic burden.[2]

Antihypertensive drugs that have direct effects on intrarenal mechanisms may have nephroprotective effects additional to those resulting from reductions in arterial BP. Whereas BP-lowering effects are common to all antihypertensive drugs; intrarenal effects differ amongst classes as well as between two drugs within same class. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have beneficial effects on proteinuria and declining renal function that appear to be mediated by factors additional to their effects on BP. These drugs acting through rennin angiotensin system (RAS) inhibition are recommended as a first-line antihypertensive approach in patients with chronic kidney disease. The addition of diuretics and calcium channel blockers (CCBs) to RAS inhibitor therapy is also considered to be a rational strategy to reduce BP and preserve renal function.[2] Calcium channel blockers are a highly heterogeneous class of compounds, and it appears that some agents are more suitable for use in patients with chronic renal disease than others. A third-generation dihydropyridine (DHP) calcium channel blockers that blocks both L and T-type calcium channels. Unlike older-generation DHPs, which preferentially act on L-type channels, third generation DHP is shown to be beneficial on intrarenal haemo dynamics, proteinuria and other measures of renal functional decline in the first clinical trials involving hypertensive patients with chronic renal failure.[3]

Lowering BP to below the autoregulatory threshold is likely to prevent malignant nephrosclerosis and ESRD in patients with uncomplicated hypertension, whereas in order to prevent the progression of renal damage, BP may need to be reduced much more in patients with chronic renal disease.

Accordingly, international guidelines recommend lowering BP to at least 140/90 mMHg in patients with uncomplicated hypertension, and to <130/80 mMHg for patients with diabetes or chronic renal disease. A goal BP of <125/75 mMHg has been recommended for patients with renal disease and proteinuria greater than 1 g/day. Although reducing BP to the goal is of primary importance in the prevention of serious renal damage, proteinuria should be monitored during the course of chronic renal disease and a protein-to-creatinine ratio of <500–1000 mg/g has been specified as another goal for antihypertensive therapy.[2]

Normally, patients undergo HD treatment three times a week; this results in alteration in extracellular fluid volume, and it is during these sessions that many patients experience large fluctuations in BP. In patients undergoing HD, The occurrence of high pre-dialysis BP can result from a number of factors; changes in extracellular volume; low compliance due to restricted salt intake.[4] sympathetic and renin–angiotensin over activation.[5] retention of uremic toxins, which can cause vasoconstriction; accumulation of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase.[6] and other factors such as parathyroid hormone secretion, erythropoietin treatment, endothelial dysfunction, and obesity associated insulin resistance.[7] It has also been noted that shortening of the dialysis session results in difficulty reaching the optimal dry weight.[8] This is believed to be related to insufficient removal of volume during the HD session, which seems to occur in spite of increasing sodium concentration in the dialysis bath. The resultant effect appears to be the maintenance of high extracellular volume and pre-dialysis BP.[9]

Achieving a lower dry weight, based on clinician best judgment, and lengthening of HD session time have proved beneficial in the management of hypertension without the use of antihypertensive medications. However, the decrease in BP by such an approach is not immediate, and it could take weeks or months before a stable reduction in BP is observed; thus, this has been labeled "the lag phenomenon".[10] It has been recently proposed that other types of dialysis procedure, such as slow but long duration dialysis (3 times 8 hours per week), short daily dialysis (2–3 hours daily, 6 times per week), or even nocturnal dialysis (6–7 overnight sessions per week), can improve the management of hypertension in HD patients.[11] Reduction of dietary salt intake, fluid restriction, and decreasing sodium concentration in the dialysis bath have also proved effective and viable

methods of lowering BP in patients undergoing HD.[12] It seems that during the dialysis session; removal of fluids results in a progressive decline in stroke volume and cardiac output as well as concomitant increase in systemic vascular resistance.[13] These modifications are associated with a reduction of vascular compliance in response to dialysis which may also contribute to the increased cardiovascular risk.[14] However, one method of dialysis that may be beneficial in decreasing BP in patients is the use of biocompatible dialysis membranes. It has been reported that the use of this technique over a course of 6 weeks decreased the mean 24- hour BP in diabetic patients.[15]

It was further postulated that one contributing factor for the antihypertensive effect in these patients was the removal of ADMA and changes in ADMA/arginine ratio resulting in "upregulation" of the nitric oxide/ arginine pathway. It is recognized that the relationship between BP and fluid removal during dialysis is influenced by the cardiac status of the patient. For example, lowering of an equal intradialytic plasma volume caused a more substantial decrease of BP in patients with cardiac failure when compared with those free of heart failure.[16] However, it must be also stated that the relationship between lowering of intradialytic plasma volume and changes in BP is a controversial topic. For instance, in a subset of patients from the hemo Study, pre- and post-dialysis BP were differently influenced by acute decrease in weight (an indicator of interdialytic fluid gain) and plasma volume (an indicator of post-dialysis volume status).[17] In this study, the pre- and post-dialysis BP was associated with larger intradialytic decreases in bodyweight but smaller intradialytic reductions in plasma volume. Each kilogram reduction in bodyweight during HD was associated with 2.95 and 1.65 mMHg higher pre-dialysis and post-dialysis systolic BP, respectively. In contrast, each 5% greater concentration of plasma volume during HD was associated with 1.5 and 2.56 mMHg lower pre-dialysis and post-dialysis systolic BP. It seems that weight and plasma volume reductions are weak determinants of the predialysis BP. This suggests most relevant contributory factors in control of BP in patients undergoing HD, are effective dry weight and cardiac status.[17]

MATERIALS AND METHOD

Study Objectives

Primary Objectives

- To observe the control of pre dialysis blood pressure
- To select safest and most effective group of anti hypertensive drugs
- To study influence of inter dialytic weight gain on the blood pressure control
- To study correlation between the duration of dialysis and the need of anti hypertensive drug treatment
- To study influence of frequency of dialysis on anti hypertensive drug treatment

Secondary Objectives

- To evaluate health related quality of life (QoL) in hypertensive patients and degree of improvement due to pharmacological therapy

Study Design: This was a single center, open label, non-randomized, observational and retrospective study. The study was carried out at Muljibhai Patel Urological Hospital, Nadiad.

Study approval: The project was approved by human research ethics committee (HREC) prior to commencement on 26/11/2011 from Muljibhaipatel society for research in nephro-urology, Nadiad.

Methodology

This was retrospective and observational study. Patient data base was accessed to collect the

necessary information for the study. Patient diagnosed with ESRD (End Stage Renal

Disease) who underwent hemodialysis along with hypertension was included in the study.

Total 100 patients who were on dialysis at least last 6 month; selected for the study.

Their records were checked to compile information such as demographic details, chest x ray,

ECG reports, blood pressure profile (pre HD BP and post HD BP), frequency and duration

of HD, dry weight and intradialytic weight gain. 6 months follow up data were collected for

anti hypertensive drug therapy.

For QoL the kidney disease outcomes quality initiative-survey form™ 1.3 health survey Questionnaire method was adopted for assessment of health and well being. Patient filled up the questionnaire; analysis of collected data was performed using paired T-test statistical method.

Patient selection criteria

Inclusion Criteria

- Patients with age ≥18 years

- Both genders
- Patients who were on the hemodialysis (HD) at least last 6 month
- Patients with systolic blood pressure greater than or equal to 130 mMHg and diastolic blood pressure greater than or equal to 80 mMHg
- Patients with Type I or II diabetes mellitus (DM)
- Patients with non-diabetic renal disease

Statistical analysis

- Patients were classified according to their pathological status (CKD and NCKD). Patients data were pooled in the excel format and analysis of the data was done by the SPSS software.
- Gender ratio was derived regarding demographic characteristics. Patients with diabetic kidney disease (DKD) and non-diabetic kidney disease (NDKD) were also compared for frequency distribution.
- Descriptive statistics methods were used for analysis. For control of pre HD systolic blood pressure (SBP) cross tabulation was used. Influence of interdialytic weight gain on BP was calculated by correlation coefficients and formula was derived from simple linear regression method.
- Influence of duration (in hours) and frequency (times/week) of hemodialysis on BP was obtained by independent sample t test. For selection safest and most effective group of drugs ANCOVA was applied.
- All p values were two sided. For all analyses, statistical significance was assumed when the two tailed probability values was less than 0.1. Continuous data were expressed as mean ± standard deviation.

RESULTS

Patient characteristics

Baseline characteristics of male and female patients are presented in Table 2.1.1. The total No. of patients (n=100) were divided in to two categories,

- Complicated Kidney Disease (CKD)
- Un-complicated Kidney Disease (UCKD). Maximum No of patients were found in the age group of 61-70 yrs (Figure 1)

Table 2.1.1: SBP of patients with CKD

Duration (Months)	Frequency(No of patients)	
	Complicated Kidney Disease(CKD) (SBP)	
	Controlled (< 130 mmHg)	Uncontrolled (≥ 130 mmHg)≥
MONTH 1	4	96
MONTH 2	1	99
MONTH 3	3	97
MONTH 4	2	98
MONTH 5	2	98
MONTH 6	5	95
%	2.83%	97.16%

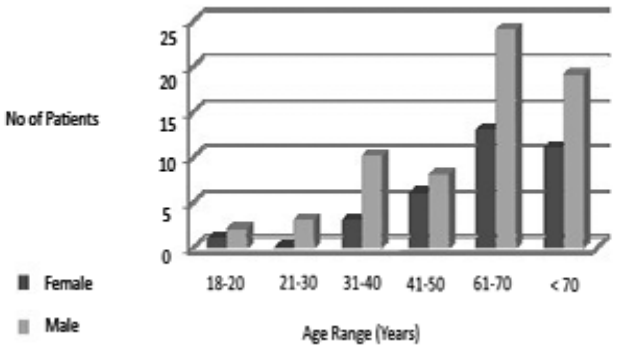

Figure 1: Different age group of patients

Table 2.1.2: DBP of Patients with CKD

Duration (Months)	frequency(no of patients)	
	Complicated Kidney Disease (CKD)(DBP)	
	Controlled (< 80 mMHg)	Uncontrolled (≥ 80 mMHg)
MONTH 1	1	99
MONTH 2	2	98
MONTH 3	2	98
MONTH 4	1	99
MONTH 5	1	99
MONTH 6	6	94
%	2.16%	97.83%

Primary end point

Control of pre dialysis blood pressure

Control of pre dialysis blood pressure was observed in patients with CKD. It was found out that CKD. Table 2.1.3 2.83% patients with CKD exhibited control of pre dialysis Systolic blood pressure (SBP) while SBP of 97.16% patients was uncontrolled (Figure 2). Table 2.1.2 Proportions of patients with and without with control of diastolic blood pressure (DBP) were found to be 2.16% and 97.83% respectively (Figure 3). Control of blood pressure was better in the patients with uncompli-

Table 2.1.3: SBP of patients with UCKD

Duration (Months)	Frequency(No of patients)	
	Uncomplicated kidney disease (UCKD) (SBP)	
	Controlled (<140 mMHg)	Uncontrolled (≥ 140 mMHg)
MONTH 1	20	80
MONTH 2	11	89
MONTH 3	15	85
MONTH 4	13	87
MONTH 5	12	88
MONTH 6	15	85
%	14.33%	85.66%

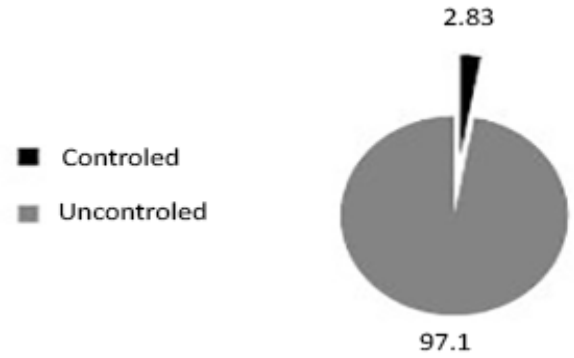

Figure 2: Control of SBP (CKD)

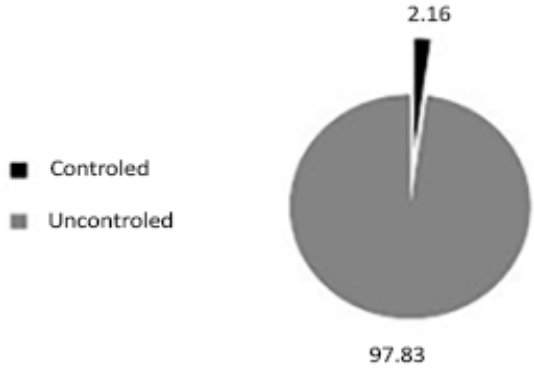

Figure 3: Control of DBP (CKD)

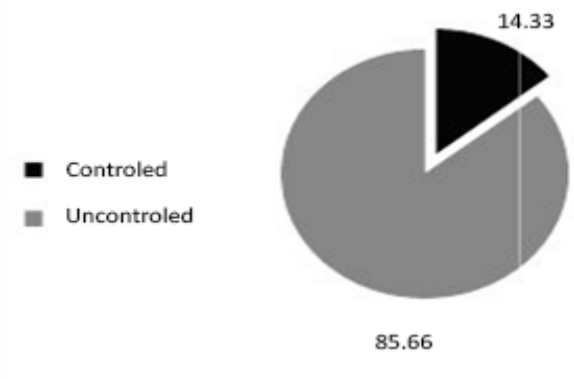

Figure 4: Control of SBP (UCKD)

Table 2.1.4: DBP of patients with NCKD

Duration (Months)	Frequency(No of patients)	
	Uncomplicated kidney disease (NCKD) (DBP)	
	Controlled (< 90 mmHg)	Uncontrolled (≥ 90 mmHg)
MONTH 1	38	62
MONTH 2	8	92
MONTH 3	30	70
MONTH 4	33	67
MONTH 5	35	65
MONTH 6	30	70
%	29.00%	71.00%

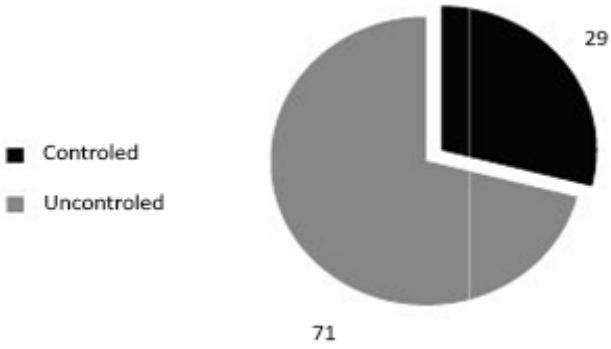

Figure 5: Control of DBP (UCKD)

cated kidney diseasentrol (UCKD) as compared to the patients with complicated kidney disease (CKD).

Similarly control of pre dialysis blood pressure was observed in patients with UCKD. It was found out that 14.33% patients with UCKD exhibited control of pre dialysis Systolic blood pressure (SBP) while SBP of 85.66% patients with UCKD were uncontrolled (Figure 4). Proportions of patients with and without control of DBP Table 2.1.4 were found to be 29.00% and 71.00% respectively (Figure 5).

Safest and most effective group of anti hypertensive drug safest

Anti-hypertensive drugs utilization in different age group of patients was recorded (Figure 6). hypertensive Calcium channel blockers (CCBs) and β-blockers were used more frequently in HD patient's blockers whereas α-blockers and Angiotensin Receptor Blockers (ARBs) were used less frequently. Blockers Vasodilators were used in two patients. Diuretics and Angiotensin Converting Enzy Converting Enzyme Inhibitors (ACEIs) each; was used in one patients only.

The effect of different group of anti hypertensive agents on blood pressure was observed (Figure 7). Results of the same indicated (P>0.1) failure of BP

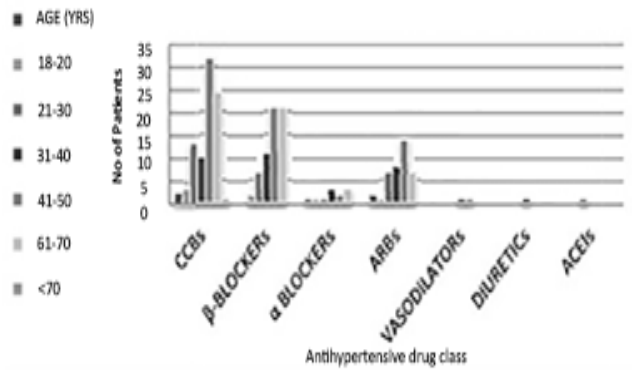

Figure 6: Anti-hypertensive drugs use in different age group patients hypertensive

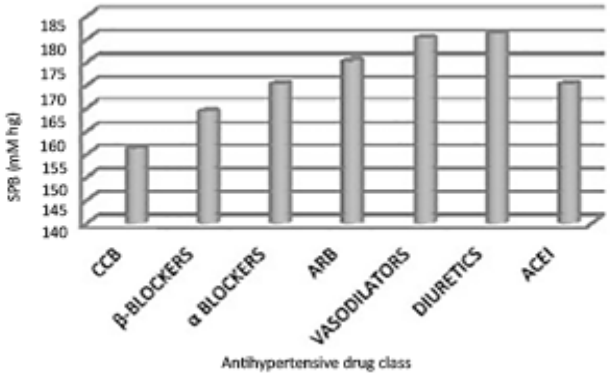

Figure 7: Effect of anti-hypertensive drugs on SB Panti

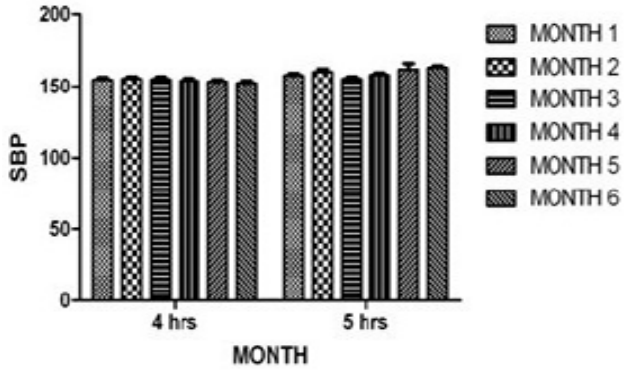

Figure 8: Effect of duration of HD on DBP

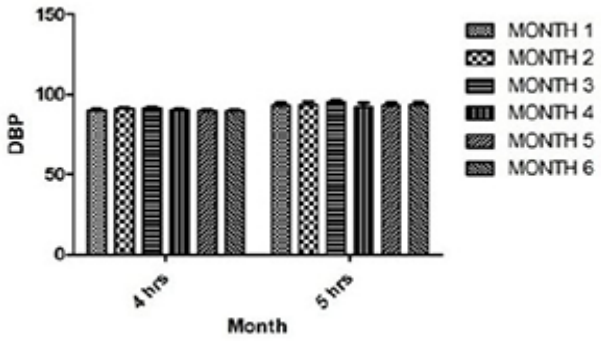

Figure 9: Effect of frequency HD on SBP and need of Anti-hypertensive drugs treatment

control in patients who underwent HD. CCBS and β-blockers showed marked decrease in BP as compared to other class of agents. α–blockers and ARBs showed less magnitude of decrease in BP. Vasodilators and diuretics did not show marked decrease in BP; While ACEIs showed marked decrease in BP but it was given in only one patient so this value is not of significance statistically.

Significant effect of interdialytic weight gain was observed on Systolic blood pressure. Table 2.3.1 [P value was 0.063 (confidence interval - 0.1)]. This relation was represented by simple linear regression equation;

$Y = B_0 + B_1X$

$SBP = 147.611+2.376*wt\ gain$

Where, Y= Systolic blood pressure

B_0 & B_1 = *coefficients*

X= weight gain

Table 2.3.1: Effect of weight gain on SBP

Parameter	Mean ± SEM	P value
Blood pressure (mmHg)	147.611 ± 3.876	0.0001
Weight gain (Kg)	2.376 ± 1.263	0.0639

Effect of duration of HD on SBP and need of Anti-Hypertensive drugs treatment.

The duration of Hemodialysis was either for 4 hrs or 5 hrs. Duration was changed as per patient's clinical condition. Effect of duration on SBP was observed (Figure 8). There was no significant difference (P>0.1) recorded during 4 months treatment. After 4 months significant difference was observed (P<0.1). Results of last two months indicates increase the need of anti hypertensive drugs with increase in duration of HD. (From 4 to 5 hrs) Similar results were also recorded for DBP with duration of HD (Figure 9).

Effect of frequency HD on SBP and need of Anti-hypertensive drugs treatment

Genrally hemodialysis was done twice or thrice a week. Frequency of HD is depends on patient's clinical condition. While studying the effect of frequency of HD on SBP (Figure 10); results indicated no significant difference (P>0.1) in BP after each month during 4 months treatment period. After 4 months period significant difference was observed in BP. After 4 months; it was found that as the frequency of HD increases (from twice to thrice a week), the systolic blood pressure was decreased and need of anti hypertensive drug treatment

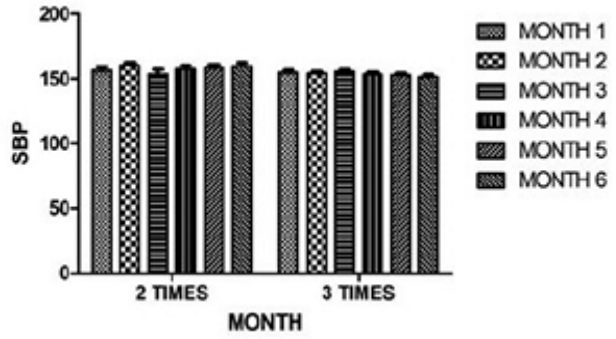

Figure 10: Effect of weekly frequency of HD on SBP

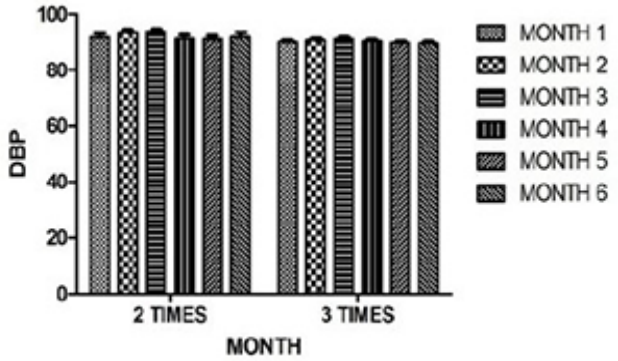

Figure 11: Effect of weekly frequency of HD on DBP

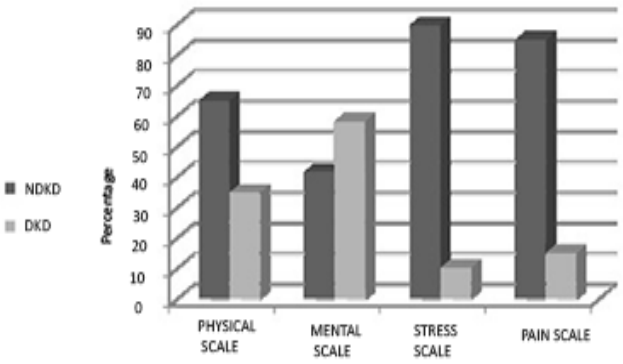

Figure 12: Dimensions for QOL in diabetic and non-diabetic patientsnon

declined. Similar results were also recorded for DBP with frequency of HD (Figure 11)

Secondary end point

Quality of life (QOL)

QOL for each patient was measured with the help of KDQOL-SF™ 1.3 health's survey. (Figure 12). The SFTM 1.3 is a generic instrument consisting four dimensions: physical state, mental/emotional state, and stress evolution and body pain (Table 3.1). Each dimension was evaluated in the range of 5 to 1. Higher score indicates better QOL. Cumulative scores for each scale is then converted in to percentage for evolution of outcome.

All of the mean SFTM 1.3 scores were calculated for all components in both the groups. At 6 month follow up, difference were seen in diabetic patients as compared to non-diabetic patients. Difference was statistically significant for physical scale (P=0.031), stress scale (P=0.050) and pain scale (P =0.021). QOL of patients evaluated by mental scale did not show any improvement but rather decline. in this parameter in patients with NDKD as compared to patients with DKD (P>0.5). Over all patients patient's with non-diabetic kidney disease had better QOL compare to the patients with diabetic kidney disease.

Table 3.1: Dimensions for QOL in diabetic and non-diabetic patients

Parameter	NDKD	DKD	P value
Physical Scale	65.05%	34.95%	0.031
Mental Scale	41.68%	58.32%	0.065
Stress Scale	89.72%	10.28%	0.050
Pain Scale	85.00%	15.00%	0.021

DISCUSSION

Hypertension is the second leading cause of ESRD after diabetes mellitus. During the period beetwen years 1990 and 2001, the incidence of ESRD caused by hypertension, increased by almost 50%.[1] The risk of ESRD increases continuously with the extent and duration of elevated blood pressure (BP). The relationship of hypertension with adverse outcomes is uncertain in the population undergoing hemodialysis. If hypertension is an etiologically significant cardiovascular risk factor in hemodialysis patients, the first step would be to assess the level of BP accurately. To manage hypertension, limiting dietary fluid intake, and individualizing dialysate sodium deliverytension, would be the initial steps as non pharmacological measures. From results it was found that SBP was controlled inadequately in patients with complicated kidney disease because they had number ofents coexisting diseases such as diabetes, anemia, bone mineral disease, vasculitis, ischemic heart disease, renal calculi, and renovascular disease. Major populations of patients undergoing hemodialysis were given erythropoeitin and divalent calcium ions.

In ESRD kidney has underwent malfunction; and was not able to produce calitriol; therefore ca++ ions were given externally. Several factors could cause of resistant hypertension, including patient noncompliance, inadequate regime, drug-to-drug interactions, pseudo resistance, secondary hypertension, and unrecognized pressor mechanisms. Due to presence of more complications, blood pressure was not controlled in HD patients. Whether control of hypertension translates

into better outcomes was not known, but obtained result suggests that hypertension should be controlled in patients undergoing hemodialysis.

Normally, patients undergo HD treatment thrice or twice a week; this results in alteration of extracellular fluid volume during HD sessions, so many patients experience large fluctuations in BP. This is believed to be related to insufficient removal of volume during the HD session, which seems to occur in spite of increasing sodium concentration in the dialysis bath.[18] The resultant effect appears to be the maintenance of high extracellular volume and pre-dialysis BP. However, the decrease in BP by such an approach is not immediate, and it could take weeks or months before a stable reduction in BP is observed. Result indicated that after 6 months, patients with thrice a week frequency showed decrease in BP as compared to the patients with low frequnecy of HD (twice per week). So, it can be concluded as the frequency of HD session increases, pre dialysis systolic blood pressure decreases.

It was reported that long duration dialysis (8 hours per week), as well as short daily dialysis (2–3hours daily) can improve the management of hypertension in HD patients.[12] Reductions of dietary salt intake, fluid restriction, and decreasing sodium concentration in the dialysis bath have also proved effective and viable methods of lowering BP in HD patients. But study results indicated that patients with longer duartion (5 hrs) of HD were having high blood pressure as compared to patients with shorter duartion (4 hrs) of HD. It is recognized that the relationship between BP and fluid removal during dialysis is influenced by the cardiac status of the patient.[16] In this study, the pre-HD BP was associated with larger interdialytic weight gain (IDWG). Interdialytic weight gain was function of higher pre HD BP. Each kilogram gain of IDW during HD was associated with 2.37 mMHg higher pre-dialysis systolic BP.

In summary, hypertension in HD is influenced by many factors associated with uremia but also by the amount of hydrosaline removal during the session, as well as cardiovascular system adaptability.[18] From the analysis of QoL it was found that; overall QoL of the patients with non diabetic kidney disease were better than patients with diabetic kidney disease. Hence it can be concluded that complications were more in the patients with diabetic kidney disease. For more significant results such study should be undertaken with larger population of patients.

CONCLUSION

Hypertension affects the vast majority of HD patients, suggesting need for the effective control or treatment of this complication. There is, however, no consensus how BP should be best possibly be recorded in daily practice (ambulatory BP mMHg) and which BP levels should be targeted as different BP levels may be set for HD patients based on their clinical status, diagnosis, age, cardiac condition, neuropathy, and other systemic condition. Therefore, it is difficult to set one BP value as ideal for all patients. Normovolaemia is the key therapeutic target for hypertension in HD patients, achieved by additional ultra filtration combined with daily dietary salt restriction (or reduced dialysate sodium concentration). Antihypertensive drugs may reduce cardiovascular complications, but it is still premature to make general recommendations for control of blood pressure in very heterogeneous population undergoing maintenance HD.

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