

Review Article

Management of hypertension in patients with end-stage renal disease leading to haemodialysis: a challenge

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ABSTRACT

The majority of the patients of end-stage renal disease (ESRD) leading to haemodialysis suffer from hypertension. Increase in blood pressure is both a cause and a consequence of chronic kidney disease and inadequate control of blood pressure in these patients increases the risk of development of left ventricular hypertrophy, congestive heart failure, stroke and other cardiovascular and neurological complications leading to high morbidity and mortality in these patients. In a meta-analysis of randomized controlled trials of antihypertensive therapy in haemodialysis patients, blood pressure lowering treatment was associated with a 29% lower relative risk of cardiovascular mortality and a 20% lower relative risk of all-cause mortality. While blood pressure control may improve cardiovascular mortality and morbidity, the management of hypertension is a big challenge in these patients especially in developing countries like India where the maintenance of optimal dry weight in between the dialysis therapy is inadequate due to high cost of hemodialysis and limited number of centers providing dialysis therapy. The aim of the present review the evidence on the optimal systolic and diastolic blood pressure in the patients on haemodialysis and the most effective drug or group of drugs that can provide adequate blood pressure control in all phases of dialysis (pre, post, intra and interdialytic phases) without complications like intradialytic hypotension or hypertension and good patient compliance.

Keywords: Antihypertensives, ESRD, Hemodialysis

INTRODUCTION

The optimal blood pressure in patients undergoing haemodialysis due to ESRD is not clearly defined by the national kidney foundation K/DOQI guidelines suggest that predialysis and postdialysis blood pressure should be < 140/90 and 130/80mmHg respectively whereas various studies suggest a mean arterial pressure of < 99 mmHg to be associated with best survival.^{1,2}

According to the USA End stage renal disease indicators project the optimal blood pressure in haemodialysis patient is when pre and post-dialysis blood pressure is <150/90 mmHg without therapy or the ambulatory day

BP <135/85 without therapy or an ambulatory night time BP <120/80 mmHg without therapy.⁴ Hypertension is defined as either systolic blood pressure >150 mmHg or diastolic blood pressure >90 mmHg.

Most patients on haemodialysis suffer from systolic hypertension which may or may not coexist with diastolic hypertension.³ The strong positive relationship of systolic blood pressure (SBP) with the risks of stroke and coronary heart disease (CHD) suggest that reduction of SBP has the potential to prevent stroke and CHD in both hypertensive and non-hypertensive patients. The relative risk of death from stroke is about 7 times greater in men with baseline SBP ≥151 mm Hg than in men with

baseline SBP <112 mm Hg. Similarly, the relative risk of death from CHD for those with the higher SBP was about 4 times greater in those with the lower systolic blood pressure.⁵ An ideal blood pressure in a haemodialysis patient would be associated with haemodialysis stability during dialysis, orthostatic tolerance after dialysis, the best cardiovascular survival and optimal health related quality of life and productivity.

Blood pressure variation in haemodialysis patient

There is marked variation in the blood pressure reading in the patients during the different phases of haemodialysis making the treatment more complicated and difficult. The blood pressure in these patients can be measured in the dialysis unit just before dialysis, during dialysis and after dialysis. However it has been found in various large studies that pre-dialysis systolic blood pressure is generally over estimated by 10 mmHg and post dialysis systolic blood pressure is underestimated by 7mmHg even though definite evidence is not yet available.⁶ Pre-dialysis systolic and diastolic blood pressure is of particular importance but interdialytic blood pressure monitoring best represent blood pressure in these patients and is considered to be the best indicator of long term cardiovascular outcome.⁷

“U” shaped mortality curve with regard to BP in haemodialysis patients

Although there is a strong positive relationship between raised blood pressure and the risk of developing left ventricular hypertrophy, congestive heart failure and cerebrovascular complications, a large observational study described a “U” shaped mortality curve with regard to blood pressure in dialysis patients. They demonstrated not only that there was increased mortality when the pre-dialysis systolic blood pressure was <110 mmHg and >180 mmHg but they also found that mortality was even higher at a lower pre-dialysis systolic blood pressure of <110 mmHg as compare to pre-dialysis systolic blood pressure of >180 mmHg.⁸ This study opens the discussion: is the haemodialysis population truly unique in that hypertension somehow provides protection against dialysis related adverse effects? The target blood pressure needs to be properly defined in this population. If the blood pressure target is absent from the guidelines, hypertension may receive inadequate medical attention. If blood pressure targets are set too low, nephrologists may expose their patients to an increase risk of intradialytic hypotension or other adverse events. We need adequately powered clinical trials to determine the risks and benefits of blood pressure control. The association of better outcomes with higher blood pressure, the so called reverse epidemiology should not be taken as causal. The target blood pressure for patients on dialysis is not clear but it is strongly recommended to avoid a drop of systolic blood pressure of greater than 30 mm Hg or post dialysis postural hypotension as it increases the mortality and hospitalization. Blood pressures of < 110/60 mm Hg

correlate significantly with the risk of death within 5 years.⁹⁻¹¹ Various observational studies in patients on haemodialysis have suggested a time dependent association between blood pressure levels and cardiovascular outcomes, with low blood pressure being associated with higher mortality rates in the short term, but lower mortality rates in the long run. Low blood pressure in dialysis patients is frequently a sign of heart failure. The United Kingdom renal association recommends a pre-dialysis blood pressure of <140/90mmHg and post dialysis blood pressure of <130/80mmHg.¹² In a one week observational study conducted by UK renal association, 36% patients achieved recommended pre-dialysis and 42% achieved recommended post-dialysis blood pressure but only 26% of the patient met both standards. This blood pressure control was achieved at the cost of increased intradialytic hypotension. The chances of developing intradialytic hypotension were maximum with alpha adrenergic blockers and least with calcium channel blockers. The lowest mortality was associated with predialysis systolic pressure of 160 to 189 mm Hg, whereas normal to low predialysis pressure values were associated with significantly increased mortality.¹³ Similarly, a study by Agarwal R, et al in haemodialysis patients also showed that the patients with the highest blood pressure have the best survival.^{14,15}

Management of hypertension in patient on haemodialysis

Several pharmacological and non-pharmacological options are available to normalize blood pressure in the patients on haemodialysis.

Lifestyle modifications

Tobacco use in patients on haemodialysis increases the risk of development of congestive heart failure by 59%, development of peripheral vascular disease by 68% and overall mortality by 37%.¹⁶⁻¹⁸

Maintenance of “dry weight”

Dry weight may be defined as the lowest attainable weight at which patients are normotensive without antihypertensive medication and do not have symptoms of postural hypotension, intradialytic or postdialytic hypotension, the criteria for assessment of dry weight are, there should not be any marked fall in blood pressure during dialysis, the pre-dialysis blood pressure at the beginning of the week should be <140/90mmHg, there should not be any peripheral edema or pulmonary congestion on chest X-ray and cardiothoracic ratio should be ≤50% in male and ≤53% in females.¹⁹ Inability of the patients to maintain optimal dry weight is one of the major cause of increase in blood pressure in the patient on haemodialysis, the optimal dry weight can be achieved by restricting the dietary salt intake if a patient follows the two gram sodium diet, an interdialytic weight gain of

1.25Kg would be expected over two days and the BP may lower by 4.2/2.0 mmHg to 5.2/3.7mmHg.²⁰ A 2.5kg or more weight gain is associated with significant rise in blood pressure.²¹ In a study conducted by Aggarwal R, et al found that a reduction of 1 kg dry weight caused a decrease of about 6.6mmHg systolic blood pressure and 3.3mmHg of diastolic blood pressure, the reduction in the systolic BP was nearly twice as much as diastolic BP, which results in attenuation of pulse pressure. Short daily dialysis and nocturnal haemodialysis also helps in maintaining optimal dry weight and blood pressure as nocturnal surge of blood pressure is observed in many dialysis patients.

Administration of antihypertensive drugs

Most classes of antihypertensive agents are appropriate for use in the haemodialysis patients, there is no published controlled trials data on specific antihypertensive agents in the dialysis patients, retrospective studies provided conflicting evidence for the possible survival benefits of various classes of antihypertensive drugs.²²⁻²⁴ General rule suggested by the various national and international agencies cannot be applied uniformly in all the patients, choice of the antihypertensive drug or a combination of drug for a patient on haemodialysis varies depending on the patient's condition, associated cardiovascular morbidity like left ventricular hypertrophy or congestive heart failure and the pharmacokinetic properties of the drugs.

Angiotensin converting enzyme inhibitors in haemodialysis patients

High renin is one of the important contributory factors for the development of hypertension and other cardiovascular morbidity in the patient on haemodialysis. Because of better safety profile and beneficial effects on cardiovascular outcome demonstrated in various clinical trials ACE inhibitors are considered as the first line drug for the treatment of hypertension in the patients on haemodialysis, apart from providing good control on blood pressure the major beneficial effects of this group of drug is that they effectively prevents development left ventricular hypertrophy.²⁵ ACE inhibitors are also effective in causing regression of left ventricular hypertrophy.²⁶ Two retrospective analysis on haemodialysis patients with acute coronary syndromes suggested the use of ACE inhibitors following myocardial infarction to be associated with lower mortality.²⁷ Another secondary analysis suggested the use of ACE inhibitors may be associated with improve survival following cardiac arrest.²⁸ A randomized controlled trial by Agarwal R et al, among maintenance dialysis patient with hypertension and left ventricular hypertrophy showed that atenolol-based (a cardioselective beta blocker) antihypertensive therapy may be superior to lisinopril-based therapy in preventing cardiovascular morbidity and all-cause hospitalizations, in this study lisinopril or atenolol each administered three

times per week after dialysis in patients of ESRD with LVH showed that hospitalizations for heart failure were worse in the lisinopril group and all-cause hospitalizations were also higher in the lisinopril group.²⁹ Most ACE inhibitors are removed during haemodialysis that needs drug supplementation after dialysis but it also decreases the chances of development of intradialytic hypotension and can be preferred in the patient where the intradialytic hypotension is a problem, as the intradialytic hypotension increases the risk of morbidity and mortality in these patients the problem of drug removal during dialysis can easily be solved by administering the long acting drug (e.g. lisinopril) thrice weekly after dialysis. Some studies have also found that use of ACE inhibitors may help in preserving the residual renal function and improve outcome in haemodialysis patients.³⁰ Another problem with the use of ACE inhibitor in the haemodialysis patient is increased risk of hyperkalemia due to inhibition of extra renal potassium loss, although some clinical trials have shown that ACE inhibitors therapy to be relatively safe with no significant effect on serum potassium and <3% incidence of symptomatic hypotension.^{31,32}

Angiotensin receptor blockers (ARB) in haemodialysis patients

Studies conducted on the antihypertensive activity and the cardio protective role of various angiotensin receptor blockers have found that administration of AT1 receptor blockers are not only effective in reducing systolic blood pressure but also significantly reduces cardiovascular events and mortality and therefor improves the long-term prognosis of the patients on haemodialysis.^{33,34} The studies have suggested that ARB improve cardiovascular outcomes by improving pulse wave velocity and reducing left ventricular hypertrophy, Valsartan (in combination with amlodipine) reduces the markers of oxidative stress in patients on haemodialysis, low doses of losartan and trandolapril improves arterial stiffness in patients on haemodialysis.^{35,36} Enalapril and Losartan causes regression of left ventricular hypertrophy in haemodialysis patients.³⁷ The other advantages of ARB over ACE inhibitor are ARB being longer acting, administered once daily and there is no dry and irritating cough which improves patient compliance. None of the angiotensin receptor blockers are removed during haemodialysis which is a problem with ACE inhibitors (Table 1) but risk of hyperkalemia with ARB is similar to ACE inhibitors.

ACE inhibitor and ARB after cardiac event in haemodialysis patients

Administration of ACE inhibitor and/or ARB caused 30% reduction in first year mortality in dialysis patients who were hospitalized with myocardial infarction.³⁸ Some small studies also demonstrated beneficial effect of giving a combination of ACE inhibitor and ARB but large clinical trial is needed to establish the fact.

Table 1: Pharmacokinetic properties of ace inhibitors and angiotensin receptor blockers (arb's) in ESRD [61].

Drug	T _{1/2} (in hours) normal	T _{1/2} (in hours) ESRD	Initial dose in haemodialysis	Maintenance dose in haemodialysis	Removal during haemodialysis
Captopril	2-3	20-30	12.5 mg q 24 h	25-50 mg q 24 h	yes
Enalapril	11	Prolonged	2.5 mg q 24 to 48 h	2.5-10 mg q 24 h to 48 h	35%
Fosinopril	12	Prolonged	10 mg q 24 h	10-20 mg q 24 h	<10%
Lisinopril	13	54	2.5 mg q 24 to 48 h	2.5-10 mg q 24-48 hours	50%
Ramipril	11	Prolonged	2.5-5 q 24h	2.5-10 mg q 24 hours	<30%
Losartan	2	4	50 mg q 24 h	50-100 mg q 24h	Nil
Candesartan	9	?	4 mg q 24 h	8-32 mg q 24 h	Nil
Irbesartan	11-15	11-15	75-150 mg q 24 h	150-300 mg q 24 h	Nil
Telmisartan	24	?	40 mg q 24 h	20-80 mg q 24 h	Nil
Valsartan	6	?	80 mg q 24 h	80-160 mg q 24 h	Nil

Table 2: Pharmacokinetic properties of calcium channel blockers in ESRD [61].

Drug	T _{1/2} (in hours) normal	T _{1/2} (in hours) ESRD	Initial dose in haemodialysis	Maintenance dose in haemodialysis	Removal during haemodialysis
Amlodipine	35-50	50 hours	2.5-5mg/d	2.5-10 mg /d	Nil
Diltiazem	4-5	Prolonged	60 mg 8-12 hourly	60-120 mg 8-12 hourly	<30%
Nifedipine	2-5	About 5	30 mg 8 hourly	30-80 mg/day	Low
Felodipine	10-15	11-16	2.5 mg once daily	2.5-10 mg/d	Nil
Verapamil	6-12	Prolonged	120 mg 8-12 hourly	120-240 mg/d	Low

Calcium channel blocker (CCB) in haemodialysis patients

Calcium channel blockers are the most commonly prescribed antihypertensive agent in the patients on haemodialysis.³⁹ Calcium channel blockers acts by binding to alpha-1 subunit of L-type calcium channel (present in the heart and vascular smooth muscles) and inhibits the entry of calcium into the myocardial and vascular smooth muscles, therefor decreasing the availability of the intra-cellular calcium. They are potent vasodilators; both dihydropyridine (e.g. amlodipine, nifedipine and felodipine) and non-dihydropyridine (Diltiazem and Verapamil) calcium channel blockers have unaltered pharmacokinetics in patients with ESRD on haemodialysis and have little dialyzability.^{40,41} The beneficial effects of CCB on cardiovascular system in the patients on haemodialysis are due to their relaxation effect on the vascular smooth muscle of coronary artery that improves systemic as well as pulmonary arterial circulation leading to improvement in coronary blood flow and reduction in oxygen demand of cardiac myocytes as a result of reduced systemic vascular resistance (vasodilatation) and blood pressure (decrease after load). Hypertension in haemodialysis patient is thought to be largely a result of volume expansion, the CCB by relaxing the smooth muscle of systemic as well as pulmonary arterial circulations decreases the vascular resistance and blood pressure in both territories. Calcium channel blockers have unique advantage in patients on haemodialysis and are effective in treating both systemic

and pulmonary hypertension.⁴² Apart from decreasing systemic and pulmonary blood pressure, calcium channel blockers by decreasing rate of discharge from SA node, suppressing ectopic pacemaker activity and increasing the refractoriness of the AV node, also prevents re-entrant excitation and cardiac arrhythmia. Some retrospective analysis suggested that the calcium channel blockers are associated with a lower risk of mortality and cardiovascular events.⁴³⁻⁴⁵ However other clinical trial comparing calcium channel blocker (Nitrendipine) to ACE inhibitor (Perindopril) failed to demonstrate a reduction in left ventricular hypertrophy with the use of a calcium channel blockers despite effectively lowering blood pressure to similar level.⁴⁶ The calcium channel blockers are not removed by haemodialysis and there is additional dose requirement following dialysis. In addition, most of the commonly used calcium channel blockers (e.g. amlodipine) are long acting requiring once daily dosing that further makes them attractive choice by the haemodialysis patients (Table 2). Amlodipine has been shown to be well tolerated, renal impairment had little effect on its pharmacokinetics, and the elimination half-life of amlodipine is about 35-50 hours which is not in patients of ESRD. The steady state concentration of amlodipine is achieved after ninth dose and the accumulation of amlodipine is not significantly different with renal function, and all these reports suggest that once daily administration of amlodipine is suitable for all degrees of renal function and that dose adjustment is not necessary in renal impairment.⁴⁷ Studies with verapamil have even suggested a reduction in intradialytic hypotension.⁴⁸ Care should be taken while prescribing

non- dihydropyridine CCB (verapamil and diltiazem) as these drugs are more myocardial selective and their combined use with beta-blockers may augment suppression of cardiac contractility and increasing the risk of bradycardia and electrical conduction defects.

Beta blockers in haemodialysis patients

Renal vasculature is richly innervated with sympathetic nerves. Increased sympathetic activity is a common finding in the patients of moderate renal failure as well as in those with end stage renal disease undergoing haemodialysis. The level of sympathetic activity is an independent predictor of total as well as cardiovascular mortality in patients with end-stage renal disease.⁴⁹ Activation of sympathetic nervous system in patients on chronic haemodialysis is well documented that makes beta-blockers as an attractive agents to reduce cardiovascular morbidity and mortality in these patients, however the value of beta-blockers in the patients on chronic haemodialysis remains unclear, the non-selective beta-blocker such as propranolol generally decreases glomerular filtration rate and renal blood flow by lowering cardiac output, thereby reflexively increasing sympathetic nervous system activity and raising systemic and renovascular resistance via stimulation of α_1 -adrenoceptors in the vascular smooth muscles and blocking β_2 -adrenoceptor mediated vasodilatation.

Most studies have shown that the chronic administration of propranolol results in the reduction of renal blood flow and glomerular filtration rate.⁵⁰ The cardioselective β -blockers (β_1 -blockers) such as metoprolol and atenolol have been studied in patients with essential hypertension with normal renal function, hypertension along with diabetic nephropathy and ESRD with dialysis and demonstrated that neither metoprolol nor atenolol produce significant reduction in GFR or renal blood flow

while effectively lowering blood pressure in patients with essential hypertension, although both can increase renovascular resistance.^{51,52} Studies with metoprolol and atenolol in patients with ESRD on chronic dialysis or after kidney transplantation have demonstrated no adverse effects on renal hemodynamics.^{53,54} Water-soluble β -blockers such as atenolol and metoprolol are dialyzable and requires supplementation to avoid exacerbation of arrhythmias following dialysis. Metoprolol is mainly metabolized by the liver and therefore does not require dose adjustment while atenolol is excreted mainly by kidneys and thus its half-life is prolonged (require one-half to three quarters of its normal dose) in haemodialysis patients owing to decreased renal clearance. However, the patients who are noncompliant with medications can be given atenolol following haemodialysis to effectively control interdialytic blood pressure.⁵⁵ In a single randomized control trial with beta blockers on survival in haemodialysis patients with NYHA class II or III congestive heart failure to standard therapy with ACEI or ARBs along with digitalis or standard therapy with carvedilol.

Carvedilol (non-selective β -blocker with additional α_1 -blocking and antioxidant activity) use was found to be associated with decreased rates of all cause mortality cardiovascular deaths and all cause hospitalizations at two years.⁵⁶ In chronic haemodialysis patients with established dilated cardiomyopathy, carvedilol has been associated with improvement in left ventricular size and function. Carvedilol is not significantly removed by dialysis (Table 3), therefore does not require additional dosing following hemodialysis, in addition to that antioxidant activity of carvedilol may provide additional benefit in these patients. The risk of hypotension, bradycardia and hyperkalemia are the only limiting factors for the use of these beta adrenergic blockers in renal compromised patient.

Table 3: Pharmacokinetic properties of beta-adrenergic blockers in ESRD [61].

Drug	T _{1/2} (in hours) normal	T _{1/2} (in hours) ESRD	Initial dose in haemodialysis	Maintenance dose in haemodialysis	Removal during haemodialysis
Atenolol	6-8	<120	25 mg q 48 h	25-50 mg q 48 h	75%
Metoprolol	3-4	3-4	50 mg twice daily	50-100 mg twice daily	High
Acebutolol	3.5	3.5	200 mg q 24 h	200-300 mg q 24 h	Yes
Carvedilol	4-7	4-7	5 mg q 24 h	5 mg q 24 h	Nil
Propranolol	2-4	2-4	40 mg twice daily	40-80 mg twice daily	<5%

Alpha-adrenergic blocker in patients on haemodialysis

Alpha-1-adrenergic blockers (Prazosin, Doxazosin and terazosin) are effective antihypertensive agents in the patients on haemodialysis. The main effect of α_1 -adrenoceptor blocker is on blood vessels, by blocking α_1 -adrenoceptors in arterioles and veins these α_1 -adrenoceptor blockers decreases peripheral vascular resistance and venous return respectively. Prazosin in addition decreases sympathetic outflow in CNS and also

suppresses baroreceptor reflex in patients with hypertension but their use alone to control hypertension in the patients on haemodialysis increases the risk of postural hypotension and intradialytic hypertension, some studies also found increased rate of cardiovascular events in patients treated by these agents.

However haemodialysis patients requiring multiple antihypertensive agents to control blood pressure, these agents can be safely used with variety of other drugs

without the need of additional dosing after dialysis. Initial low dose (1mg/day) and nocturnal dosing of long acting agents (Table 4) will minimize the occurrence common

adverse effects like postural hypotension and syncopal attack by these drugs.

Table 4: Pharmacokinetic properties of other antihypertensive agents in ESRD [61].

Drug	T _{1/2} (in hours) normal	T _{1/2} (in hours) ESRD	Initial dose in haemodialysis	Maintenance dose in haemodialysis	Removal during haemodialysis
Pharmacokinetic properties of α_1 -adrenergic antagonists					
Prazosin	2-3	2-3	1 mg at bedtime	1-5 mg twice a day	Nil
Doxazosin	20	15-22	1 mg at bedtime	1-8 mg at bed time	Nil
Terazosin	9-12	9-12	1 mg at bed time	1-20 mg at bed time	Nil
Pharmacokinetic properties of central sympatholytic agent.					
Clonidine	10-12	18-41		0.1-0.4 mg twice daily.	<5%
Pharmacokinetic properties of direct vasodilators:					
Hydralazine	One	7-16	10 mg every 8h	10-100 mg every 8h	Nil
Isosorbide dinitrate	3-6	?	5 three times a day	5-40 mg three times a day	Partially
Minoxidil	4	?	5 mg/d	5-100 mg/d	Partially

Central sympatholytic agents in haemodialysis patients

Central sympatholytic agents produces their antihypertensive effect mainly by decreasing the central sympathetic outflow, their use alone for the treatment of hypertension in dialysis patients is less common because of high rate of intolerable side effects like sedation, dry mouth, erectile dysfunction in males and rebound hypertension they may produce, but they are commonly used as add-on drug for the treatment of hypertension that is not properly controlled by drugs like CCB, ACE inhibitors and ARB. Clonidine (α_2 -adrenergic agonist) is particularly used in the patients of haemodialysis with severe hypertension or difficult to control hypertension. Recently developed transdermal patch of clonidine that can be applied on skin at weekly interval while avoiding frequent dosing is preferred and well tolerated by some patients but are not universally effective as some patients find them difficult to keep in place during strenuous activity and with showering.⁵⁷

Diuretics in haemodialysis patients

Diuretic are not very effective in decreasing blood pressure in patients of ESRD leading to haemodialysis because most of the diuretic are secreted in the proximal tubule of the nephron for their activity therefor diuretics acting on the distal tubule (thiazide and potassium-sparing diuretics) loses their effectiveness when creatinine clearance decreases to < 30-50ml/min and the more potent loop diuretics (furosemide) retains their effectiveness at low creatinine clearance (>5ml/min).⁵⁸ Furosemide is effective in controlling interdialytic weight gain by increasing urine output in the patients with residual renal function, this drug also lower relative risk of pulmonary edema in these patients by releasing prostaglandin from kidney leading to vasodilatation and

decrease in both systemic and pulmonary vascular pressure, therefor furosemide should not be discontinued on putting the patient on dialysis or can be given in patients on high risk of developing pulmonary hypertension and pulmonary edema.

Direct vasodilators in haemodialysis patients

Direct vasodilators (e.g. minoxidil) are also effective antihypertensive agent, however if they are used alone for the treatment of hypertension, their effect is lost in due course of time due to various compensatory mechanisms therefor, to maintain the efficacy of these drugs on prolonged use the vasodilator can be used in combination with other drug like beta-adrenergic blocker to decrease tachycardia produced by these vasodilators but the other adverse effects produced by these drugs like hirsutism, pericardial effusion and edema (by minoxidil) needs careful monitoring.⁵⁹ Hydralazine and isosorbide dinitrate are other direct vasodilators that are effective in lowering blood pressure in these patients but are only used in resistant or refractory hypertension because of frequent dosing and other side effects.

Resistant hypertension and its treatment in patients on haemodialysis

Resistant hypertension in the patients on haemodialysis is defined as blood pressure remaining above the goal in spite of concurrent use of three antihypertensive agents from different classes. The common causes for the development of resistant hypertension in these patients are increasing cysts in polycystic kidney disease, renovascular hypertension, the use of non-steroidal anti-inflammatory drugs (NSAIDs) and hyper-activation of the sympathetic nervous system.⁶⁰ The treatment options are use of clonidine (transdermal at weakly intervals) or

minoxidil with beta blocker. Spironolactone (post dialysis) improves blood pressure control in these patients but there is risk of hyperkalemia. Future hope for the treatment of resistant hypertension in these patients lies on baroreflex activation therapy (BAT) and renal denervation therapy.

Intradialytic hypertension

About 5-15% patient on haemodialysis develops an acute rise of blood pressure during dialysis therapy the possible explanation of this rise in blood pressure are removal of antihypertensive agents during dialysis, changes in sodium levels due to removal of fluids, activation of the renin-angiotensin-aldosterone system, over activity of the sympathetic nervous system, endothelial cell dysfunction. Adequate sodium and water removal, reducing sympathetic hyperactivity and changing to non-dialyzable antihypertensive medications may be helpful in this condition.

CONCLUSIONS

Cardiovascular disease is the most common cause of death in patient on chronic haemodialysis therapy, despite the advances in dialysis therapy the morbidity and mortality from cardiovascular disease in patients undergoing haemodialysis remains substantially unchanged, the adequate control of blood pressure is crucial as both low and high blood pressure are undesirable in these patients. Inadequate dialysis (due to poor economic condition of patients and scarcity of state funded dialysis centers) leading to extracellular volume expansion is the major contributing factor for the poor blood pressure control in developing countries.

Although ACE inhibitors, ARB and beta-blockers appear to be attractive agents due to their independent cardiovascular benefits calcium channel blockers (e.g. amlodipine) are preferred antihypertensive agent because of their better efficacy in patients with expanded plasma volume as well as less incidence of intradialytic complications (e.g. hypotension) and good patients compliance.

The other necessary measures that should be considered in hypertensive patients undergoing haemodialysis are lifestyle modification, dietary salt and fluid restriction, use of appropriate longer acting antihypertensive agents that can preferentially be administered at night to control nocturnal surge of blood pressure observed in many dialysis patients and use of renally eliminated agent (lisinipril or atenolol) thrice weekly following haemodialysis under direct supervision in noncompliant patients.

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