



Efficacy of various antihypertensive drugs in the treatment of hypertension in the patients of end-stage renal disease leading to hemodialysis- A retrospective study.

KEYWORDS

Hemodialysis, Antihypertensive agent, Amlodipine

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ABSTRACT

Introduction: Cardiovascular complications are the leading cause of morbidity and mortality in the patients of end-stage renal disease leading to hemodialysis. Majority of these patients suffers from hypertension and adequate control of blood pressure is a challenge in these patients because of multifactorial etiology and complicated pharmacokinetic changes in these patients. The present study aims is to find out the best possible drug or combination of drugs that can provide better control of blood pressure and improve the quality of life of these patients. **Methodology:** A retrospective study was carried out on the patients who attended the hemodialysis unit of Hakeem Abdul Hamid Centenary hospital from July 2015 to June-2016 (one year), data on antihypertensive drugs and blood pressure control (Pre-dialysis and post-dialysis) were recorded and analyzed. **Result:** 68.75% patients on hemodialysis were suffering from hypertension and were on antihypertensive medication. A combination of Amlodipine and clonidine were the most frequently prescribed antihypertensive agents. Muscle cramps an acute rise in blood pressure and hypotension were the most frequently encountered intradialytic complications in these patients. **Conclusion:** Although a combination of Amlodipine and Clonidine was most frequently prescribed antihypertensive medication in these patients these drugs were associated with intradialytic complications like muscle cramps and hypotension. Amlodipine with beta-adrenoceptor blocker (Metoprolol or Bisoprolol) provided best control of blood pressure in these patients with least intradialytic complications.

Introduction

Cardiovascular diseases are the leading cause of morbidity and mortality in the patients of end stage renal disease (ESRD) leading to hemodialysis. Despite the advances in dialysis therapy the morbidity and mortality from cardiovascular diseases in these patients remains substantially unchanged. Hypertension is both a cause and a consequence of chronic kidney disease and the adequate control of blood pressure is equally difficult that increases the risk of development of left ventricular hypertrophy, congestive heart failure, stroke and other cardiovascular and neurological complications. In a meta-analysis of randomized controlled trials of antihypertensive therapy in hemodialysis 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 [1]. The causes of rise in the blood pressure in these patients are multifactorial such as inappropriately high renin secretion, over activity of sympathetic nervous system, alteration in endothelin and nitric oxide, positive sodium balance due to increased intake, decreased excretion and hypertonic dialysate increasing interdialytic thirst [2]. The uremic metabolites activating chemoreceptors within the kidney, Erythropoietin therapy, and hyperparathyroidism [3,4] are the other causes. In developing countries the high cost of dialysis therapy and the scarcity of state funded health facilities are responsible for inadequate hemodialysis leading to inappropriately high weight gain (fluid accumulation) during interdialytic period and poor control of blood pressure.

Drug utilization study: According to WHO, Drug utilization study is defined as "the marketing, distribution, prescription and use of drugs in society with special emphasis on the resulting medical, social and economic consequences" (WHO, 1977). It is a onetime study to assess the appropriateness of

drug therapy. These types of studies are useful for implementation of the rational use of drugs among population in both private and public healthcare. It is important to realize that inappropriate use of drugs represent a potential hazard to the patients along with an unnecessary expense.

Process of drug utilization review: The drug utilization study is grouped into (a) The retrospective drug utilization review where the data on prescribing and dispensing of drugs are evaluated after the drug has been dispensed in a given health care environment (b) the Prospective drug utilization study, evaluates data on drug prescribing and /or dispensing prior to prescribing and dispensing in a given health care environment and can directly influence patient's treatment outcome and (c) Concurrent drug utilization review, evaluates data on prescribing and use of drugs during the course of treatment and involves the ongoing monitoring of drug therapy, that can influence the course of drug therapy [5].

The aim of the present study is to find out the commonly prescribed antihypertensive agents to the patients undergoing hemodialysis and to compare their efficacy and safety in this population of patients. The present study also aims to find out the common causes of therapeutic failure in these patient and their solution if possible.

Study design and Methodology

A single center retrospective study was carried out on the patients who attended the hemodialysis unit of Hakeem Abdul Hamid Centenary hospital, a teaching hospital attached to Hamdard institute of medical sciences & research, Jamia Hamdard, New Delhi. Medical record of all the patients who received dialysis therapy between July-2015 to June-2016 (one year) and received at least eight dialysis sessions (for one month) in hemodialysis unit were included in the study and

further analyzed for their demographic variables, etiology of renal disease leading to end-stage renal disease, co-morbid conditions, blood pressure readings of hypertensive patients, (both before and after dialysis) frequency of dialysis received per week and intradialytic complications. Details of antihypertensive drugs prescribed were recorded (name of the drug, dose, dosage form, route of administration, frequency of administration, indications for use and duration of therapy). The blood pressure (pre-dialysis and post dialysis) recorded were taken from patient record file.

Data were evaluated by Microsoft excel for analysis and descriptive statistics.

Result

Overall 135 patients received hemodialysis therapy in the dialysis unit of Hakeem Abdul Hamid Centenary hospital during the study period, among these patients 23 patients were excluded from the study either due to the non-availability of sufficient data or they left the dialysis center after receiving only few dialysis therapy (<1 month). Altogether 112 hemodialysis patients fulfilled our inclusion criteria and were included in our statistical analysis. Among the study population 76 (67.85%) were male and 36 (32.14%) were female, the maximum number of patients were from the age group 41-60 years (41.07%) followed by the patients of age group 21-40 years (31.25%) and patients of > 60 years (25.89%) (Fig. 1).

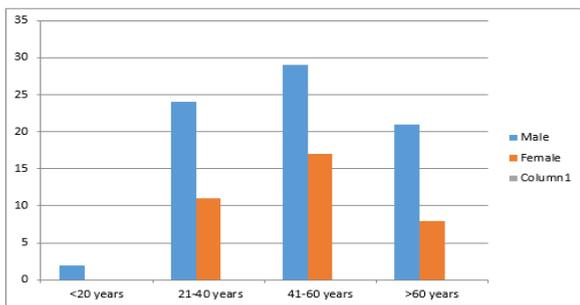


Fig. No.1: Age & gender distribution of hemodialysis patients.

Primary cause of ESRD leading to dialysis: Hypertension is the most common cause of ESRD leading to hemodialysis (41.96%) followed by diabetes mellitus (25%) whereas in 16.07 % patients the cause of ESRD leading to dialysis is not known (Table- 1).

Table No.1: Primary cause of ESRD leading to dialysis.

Primary cause	Number of patients	%
Hypertension	47	41.96
Diabetes mellitus	28	25
Obstructive nephropathy	8	7.14
Chronic Glomerulonephritis	7	6.25
Polycystic kidney disease	4	3.57
Other causes (unknown etiology)	18	16.07

Chronic comorbidity in the patients of ESRD leading to hemodialysis: Hypertension topped the list of all comorbidity (57.03%) followed by diabetes mellitus (25.18) and coronary artery disease (3.7%) (Table-2).

Table No.2: Chronic comorbidity in dialysis patients.

Co-morbid conditions	Number of patients	% of patients
Hypertension	77	68.75
Diabetes mellitus	28	25
Coronary artery disease	6	5.35
Hepatitis-C	1	0.89

Pattern of antihypertensive agents prescribed in the patients on hemodialysis: out of total 135 patients included in the study, 77 (57.03%) were hypertensive and were receiving antihypertensive medication. A combination of Amlodipine and Clonidine were the most frequently prescribed agents (28.57%) followed by Amlodipine with clonidine + furosemide (22.07%) and Amlodipine with beta-adrenoceptor blocker (18.18%) (Table-4).

Table No.4: Pattern of antihypertensive agents prescribed.

Antihypertensive drug / combination of drugs	Number of patients (Total No: 77)	(%) of patients
Amlodipine + Clonidine	22	28.57
Amlodipine + Clonidine + Furosemide	17	22.07
Amlodipine + Metoprolol (Bisoprolol)	14	18.18
Amlodipine	8	10.38
Amlodipine + Prazocin	5	6.49
Telmisartan or Candesartan	5	6.49
Amlodipine + Monoxidil	3	3.89
Torseamide	3	3.89

Efficacy of various antihypertensive drugs or combination of drugs in Blood pressure control: the average blood pressure control in all phases of dialysis (inter-dialysis, pre-dialysis and post dialysis) were best provided by a combination of amlodipine with beta-adrenoceptor blocker with minimum inert-dialysis complications followed by amlodipine with clonidine (table-5).

Table-5: Efficacy of antihypertensive drugs in controlling on pre-diastric and post diastric BP.

Drugs	Average Inter-dialysis BP (in mmHg)		Average Pre-dialysis BP (in mmHg)		Average Post-dialysis BP (in mmHg)		Intra-dialytic complications
	Systolic BP	Diastolic BP	Systolic BP	Diastolic BP	Systolic BP	Diastolic BP	
Amlodipine + Clonidine	166	84	180	94	160	76	Muscle cramps + Acute rise in BP during dialysis
Amlodipine + Clonidine + Furose	150	76	166	92	136	64	Muscle cramps Hypotension Shivering

Amlodipine + Metoprolol (Bisoprolol)	144	76	160	80	130	88	Muscle cramps
Amlodipine	140	90	156	94	160	88	Rise in BP during dialysis
Amlodipine + Prazosin	160	80	160	90	130	64	Muscle cramps + Shivering
Telmisartan or Candisartan	138	90	144	90	132	84	NON
Amlodipine + Monoxidil	160	90	160	100	140	90	Muscle cramps + Back pain
Torsemide	130	70	132	80	124	74	Hypotension + Shivering

Discussion

The mean age of patient in our study was 42.94 ± 15.97 , the previous Indian studies reported 47.4 ± 14.9 years [6] and 46.5 ± 16.5 years [7]. This indicates that the trend of chronic kidney disease is shifting downward towards the younger age group which may be due to adaptation of some unhealthy life style which predisposes the persons to early development of the primary diseases like hypertension and diabetes mellitus leading to early development of chronic kidney disease as complication. The average age of development of end stage renal disease (ESRD) and need of renal replacement therapy is much lower in India as compared to other countries (54.6 ± 12.2 years in Serbia and 60.6 ± 16.0 years in USA) [8,9]. Predominance of male in our study is similar to earlier reports [10, 11]. Although hypertension and diabetes mellitus were the most common primary disease that lead to chronic kidney disease and finally ESRD which was similar to other Indian studies [14,15]. There was a significant number of patients (11.11%) in which the cause of end-stage renal disease was obstructive nephropathy which would have been prevented by early diagnosis and treatment.

Anti-hypertensive medication and blood pressure control in hemodialysis patients: The majority of the patients of end-stage renal disease (ESRD) leading to hemodialysis suffer from hypertension. Although an increase in the blood pressure is both a cause and a consequence of chronic kidney disease. It predisposes these patients to 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 [16, 17, 18, 19]. In the present study although all hypertensive patients were receiving antihypertensive medications yet their blood pressure were not adequately controlled which may be due to the failure to maintain optimal dry weight [20]. A 2.5kg or more weight gain is associated with significant rise in blood pressure [21, 22]. In this study only 14.2% were achieving 2 Kg interdialytic weight gain, in rest of the patient the average interdialytic weight gain was 3 to 5 kg. The contributory factors of the rise in blood pressure may the poor compliance of patient to restriction of salt intake and inadequate dialysis. Adequate hemodialysis and restricting the dietary salt intake are beneficial in controlling blood pressure in these patients, 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 [23]. High renin is one of the important contributory factor for the development of hypertension and other cardiovascular morbidity in the patient on hemodialysis and many clinical trials have demonstrated that angiotensin converting enzyme inhibitors are safe and effective in hemodialysis patients [24,25]. In our study Angiotensin receptor blocker therapy provided best blood pressure control (in all phases of dialysis) with minimum intradialytic complications but their use were less and ACE inhibitors were not used at all which may be due to the fact that most of the ACE inhibitors are removed during hemodialysis. Moreover ACEI and ARBs are associated with an increased risk of hyperkalemia potentially due to its ability of inhibiting extrarenal potassium loss [26] and it is more dangerous in the patients where there are chances of inadequate dialysis.

CALCIUM CHANNEL BLOCKERS (CCB) IN HEMODIALYSIS PATIENTS:

Calcium channel blockers are the most commonly prescribed antihypertensive agents in the patients on hemodialysis [27, 40, 41]. 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 hemodialysis and have little dialyzability [28, 29]. Hypertension in hemodialysis 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 circulation decreases the vascular resistance and blood pressure in both territories. Calcium channel blockers have unique advantage in patients on hemodialysis and are effective in treating both systemic and pulmonary hypertension [30]. Apart from decreasing systemic and pulmonary blood pressure, calcium channel blockers by decreasing the 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 [31, 32, 33]. 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 may increase the risk of bradycardia and electrical conduction defects.

BETA BLOCKERS IN HEMODIALYSIS PATIENTS: Activation of sympathetic nervous system in patients on chronic hemodialysis is well documented that makes beta-blockers as an attractive agents to reduce cardiovascular morbidity and mortality in these patients. The cardioselective β_1 -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 [34, 35]. Studies with metoprolol and atenolol in patients with ESRD on chronic dialysis or after kidney transplantation have demonstrated no adverse effects on renal hemodynamics [36, 37]. Water-soluble β_1 -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 hemodialysis patients owing to decreased renal clearance. However, the patients who are noncompliant with medications can be given atenolol following hemodialysis to effectively control interdialytic blood pressure [38].

ALPHA-ADRENERGIC BLOCKER IN PATIENTS ON HEMODIALYSIS: Alpha-1-adrenergic blockers (Prazosin, Doxazosin and terazosin) are effective antihypertensive agents in the patients on hemodialysis but their use alone to control hypertension in the patients on hemodialysis 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 hemodialysis patients requiring multiple antihypertensive agents to control blood pressure, these agents can be safely used with variety of other drugs.

CENTRAL SYMPATHOLYTIC AGENTS IN HEMODIALYSIS 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 is particularly used in the patients of hemodialysis with severe hypertension or difficult to control hypertension.

Conclusion

Majority of the patients with end-stage renal disease leading to hemodialysis needs antihypertensive medication [40]. Although angiotensin converting enzyme inhibitor and angiotensin receptor blockers are considered as first line in drug in these patients especially in the patients with cardiomyopathy but these drugs are not frequently prescribed because of their dialyzability (ACE inhibitors) and relatively poor efficacy. Although in our study a combination of amlodipine with clonidine and/or furosemide were the most frequently prescribed agents they were frequently associated with intradialysis complication whereas a combination of amlodipine with beta-adrenoceptor blocker provided adequate control of blood pressure in all phases of dialysis with least intra-dialysis complication. Volume overload due to inadequate dialysis is the main cause of poor control of blood pressure in these patients therefore calcium channel blockers are reported to be the drug of first choice in patients with volume overload [30].

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