Efficacy of Various Antihypertensive Drugs in the Treatment of Hypertension in the Patients of End-Stage Renal Disease Leading to Haemodialysis- A Retrospective Study

Razi Ahmad¹, Sana Rehman¹, Anwar Habib² and Faran Naim³

¹Department of Pharmacology, HIMSR, Jamia Hamdard, New Delhi, India
²Department of Medicine and Head Dialysis Unit, HIMSR, Jamia Hamdard, New Delhi, India
³Department of Clinical, Sir Ganga Ram Hospital, New Delhi, India

Corresponding author: Razi Ahmad, Department of Pharmacology, HIMSR, Jamia Hamdard, New Delhi 110062, India, Tel: 011-2605 5715; E-mail: rahmad50@gmail.com

Received date: October 04, 2016; Accepted date: October 27, 2016; Published date: November 03, 2016

Copyright: © 2016 Ahmad R, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License; which permits unrestricted use, distribution, and reproduction in any medium; provided the original author and source are credited.

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 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 Haemodialysis 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 haemodialysis 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.

Keywords: Haemodialysis; Antihypertensive agent; Amlodipine

Introduction

Cardiovascular diseases are the leading cause of morbidity and mortality in the patients of end stage renal disease (ESRD) leading to Haemodialysis. 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 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 [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 Haemodialysis 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” [5]. 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 Haemodialysis 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 patients and their solution if possible.

Study Design and Methodology

A single center retrospective study was carried out on the patients who attended the Haemodialysis unit of Hakeem Abdul Hamid Centenary hospital, a teaching hospital attached to Hamdard institute of medical sciences and 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 haemodialysis 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

Patient characteristics

Overall 135 patients received Haemodialysis 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 haemodialysis 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%) (Figure 1).

Primary cause of ESRD leading to dialysis

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

Chronic comorbidity in the patients of ESRD leading to haemodialysis

Hypertension topped the list of all comorbidity (57.03%) followed by diabetes mellitus (25.18) and coronary artery disease (3.7%) (Table 2).
Pattern of antihypertensive agents prescribed in the patients on haemodialysis

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 3).

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 4).

Discussion

The mean age of patient in our study was 42.94 ± 15.97; the previous Indian studies reported 47.4 ± 14.9 years and 46.5 ± 16.5 years [6,7]. 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 [12-15]. There were 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 haemodialysis patients

The majority of the patients of end-stage renal disease (ESRD) leading to Haemodialysis 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 [16-19]. 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 2.5 kg 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 haemodialysis 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 1.25 kg would be expected over two days and the BP may lower by 4.2/2.0 mmHg to 5.2/3.7 mmHg [4].

High renin is one of the important contributory factor for the development of hypertension and other cardiovascular morbidity in the patient on haemodialysis and many clinical trials have demonstrated that angiotensin converting enzyme inhibitors are safe and effective in haemodialysis patients [23,24]. 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 haemodialysis. Moreover ACEI and ARBs are associated with an increased risk of hyperkalemia potentially due to its ability of inhibiting extrarenal potassium loss [25] and it is more dangerous in the patients where there are chances of inadequate dialysis.

**Calcium channel blockers (ccb) in haemodialysis patients**

Calcium channel blockers are the most commonly prescribed antihypertensive agents in the patients on haemodialysis [16,26]. 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 [27,28]. Hypertension in haemodialysis patient is thought to be largely a result of volume expansion, the CCB by relaxing the smooth muscle of systemic as we as pulmonary arterial circulation 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 [16].

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 [29-31]. Studies with verapamil have even suggested a reduction in intradialytic hypotension [16]. 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 haemodialysis patients**

Activation of sympathetic nervous system in patients on chronic Haemodialysis is well documented that makes beta-blockers as attractive agents to reduce cardiovascular morbidity and mortality in these patients. The cardioselective β-blockers (β₁-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 [32,33]. Studies with metoprolol and atenolol in patients with ESRD on chronic dialysis or after kidney transplantation have demonstrated no adverse effects on renal hemodynamics [34,35]. Water-soluble β-blockers such as atenolol and metoprolol are dialyzable and require 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 [28,36].

**Alpha-adrenergic blocker in patients on haemodialysis**

Alpha-1-adrenergic blockers (Prazosin, Doxazosin and terazosin) are effective antihypertensive agents in the patients on Haemodialysis 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.

**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 is particularly used in the patients of Haemodialysis with severe hypertension or difficult to control hypertension.

**Conclusions**

Majority of the patients with end-stage renal disease leading to Haemodialysis needs antihypertensive medication [16]. 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 amiodpine with clonidine and or furosemide were the most frequently prescribed
agents they were frequently associated with intra-dialysis 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 [29].

References

1. Heerspink HJ, Ninomiya T, Zoungas S, de Zeeuw D, Gروبbee DE, et al. (2009) Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomized controlled trials. Lancet 373: 1009-1015.

2. de Paula FM, Peixoto AJ, Pinto LV, Dorigo D, Patricio PJ, et al. (2004) Clinical consequences of an individualised ischaemic preconditioning in haemodialysis patients. Kidney Int 66: 1232-1238.

3. Locatelli F, Covic A, Chazot C, Leunissen K, Luno J, et al. (2004) Hypertension and cardiovascular risk assessment in dialysis patients. Nephrol Dial Transplant 19: 1036-1068.

4. Fishbane S, Natke E, Maesaka JK (1996) Role of volume overload in dialysis-refractory hypertension. Am J Kidney Dis 28: 257-261.

5. WHO (1977) Drug utilization review. World Health Organization, Geneva.

6. Rizvi SA, Manzoor K (2002) Causes of chronic renal failure in Pakistan: a single large center experience. Saud J Kidney Dis Transpl 13: 376-379.

7. Vikrant S, Machhan P, Pandey D (2004) Hemodialysis experience at a tertiary care hospital in Himachal Pradesh. Indian J Nephrol 14: 128-129.

8. Dordevic V, Stojanovic M, Stefanovic S (1999) Adequacy of hemodialysis in a large university affiliated dialysis center in Serbia. Facta Universitatis 6: 107-111.

9. Bailie GR, Eisele G, Liu L, Roys E, Kiser M, et al. (2005) Pattern of medication use in the RRI-CKD: focus on medications with cardiovascular effects. Nephrology Dialysis Transplant 20: 1110-1115.

10. Alexiou C, Ayalew O, Abbas A, Olotuyin AI (2006) Chronic renal failure at the Olabisi Onaboj University teaching hospital, Sagamu, Nigeria. Afr Health Sci 6: 132-138.

11. Dash SC, Agarwal SK (2006) Incidence of chronic kidney disease in India. Nephrol Dial Transplant 21: 232-233.

12. Hecking E, Bragg-Gresham JL, Rayner HC, Pisoni RL, Andreucci VE, et al. (2004) Hemodialysis prescription, adherence and nutritional indicators in five European countries: result from the dialysis outcomes and practice patterns study (DOPPS). Nephrol Dial Transplant 19: 100-107.

13. Ohawa M, Kato K, Itai K, Onoda T, Konda R, et al. (2005) Cardiovascular risk factors in hemodialysis patients. J Epidemiol 15: 46-59.

14. Modi G K, Jha V (2006) Incidence of end-stage renal disease in India: a population-based study. Kidney Int 70: 2131-2133.

15. Tozawa M, Iseki K, Iseki C, Oshiro S, Higashiusato Y, et al. (2002) Analysis of drug prescription in chronic hemodialysis patients. Nephrol Dial Transplant 17: 1819-1824.

16. Agarwal R, Nissenson AR, Bailie D, Coyne DW (2003) Trout JR. Prevalence, treatment and control of hypertension in chronic hemodialysis patients in the United States. Am J Med 115: 291-297.

17. Mazzuchi N, Carbonell E, Fernandez CJ (2000) Importance of blood pressure control in hemodialysis patient survival. Kidney Int 58: 2147-2154.

18. Takada A, Toda T, Fujii T, Shinohara S, Sasaki S, et al. (2005) Discordance of influence of hypertension on mortality and cardiovascular risk in hemodialysis patients. Am J Kidney Dis 45: 112-118.

19. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, et al. (1996) Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. Kidney Int 49: 1379-1385.

20. Inrig JK, Patel UD, Gillespie BS, Hasselbalb V, Himmelfarb J, et al. (2007) Relationship between interdialytic weight gain and blood pressure among prevalent hemodialysis patients. Am J Kidney Dis 50: 108-118.

21. He FJ, MacGregor GA (2002) Effect of modest salt reduction on blood pressure: A meta-analysis of randomized trial. Implications for public health. J Hum Hypertens 16: 761-770.

22. Rocco MV, Van G, Heyka RJ, Benz R, Cheung AK, et al. (2001) Risk factors for hypertension in chronic hemodialysis patients, baseline data from the HEHO study. Am J Nephrol 21: 280-288.

23. Agarwal R, Lewis R, Davis JL, Becker B (2001) Lisinopril therapy for hemodialysis hypertension. Hemodynamic and endocrine responses. Am J Kidney Dis 38: 1245-1250.

24. Zannad F, Kessler M, Lebert P, Grünfeld JP, Thuillez C, et al. (2006) Prevention of cardiovascular events in end-stage renal disease: Result of randomized trial of fosinopril and implications for future study. Kidney Int 70: 1318-1324.

25. Knoll GA, Sahgal A, Nair RC, Graham J, van Walraven C, et al. (2002) Renin-angiotensin system blockade and increased risk of hyperkalemia in chronic hemodialysis patients. Am J Med 112: 110-114.

26. Branten AJ, Hilbrands LB, Van Hamersvelt HW (1998) Renal and systemic effects of atenolol and tertanol in renal transplant recipients on cyclosporine. Nephrol Dial Transplant 13: 423-426.

27. Agarwal R (2006) Management of hypertension in hemodialysis patient. Hemodialysis International 10: 241-248.

28. No authors listed (1997) The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood pressure. Arch Inten Med 157: 2413-2446.

29. Kungys G, Naujoks H, Wanner C (2003) Pharmacokinetics of amlodipine in hypertensive patients undergoing hemodialysis. Eur J Clin Pharmacol 59: 291-295.

30. Zachariah PK, Moyer TP, Theobald HM, Frantz RP, Kurtz SB, et al. (1991) The pharmacokinetics of racemic verapamil in patients with impaired renal function. J Clin Pharmacol 31: 45-53.

31. Satoskar RS, Rege N, Bhardarck SD (2015) Pharmacology and pharmacotherapeutics (24th edn). Elsevier, Netherlands.

32. Tepel M, Hopfenueller W, Solzhe A, Maler A (2008) Effect of amlodipine on cardiovascular events in hypertensive hemodialysis patients. Nephrol Dial Transplant 23: 3605-3612.

33. Kestenbaum B, Gillen DL, Sherrard DJ, Seliger S, Ball A, et al. (2002) Calcium channel blocker use and mortality among patients with end-stage renal disease. Kidney Int 61: 2157-2164.

34. Epstein M, Oster JR (1985) Beta blockers and renal function: A reappraisal. J Clin Hypertens 1: 85-99.

35. Sugino G, Barg AP, O’Connor DT (1984) Renal perfusion is preserved during cardioselective beta-blockade with metopolol in hypertension. Am J Kidney Dis 3: 357-361.

36. Ljungman S, Wilsstrand J (1993) Effects of long-term antihypertensive treatment and aging on renal function and albumin excretion in primary hypertension. Am J Hypertens 6: 554-563.