Alpha-blockers in Renal Disease: Appraisal of Evidence

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Introduction

In patients of chronic kidney diseases (CKD), the significance of cardiovascular complications is well known. Progressive decline in renal function is associated with increasing rates of hypertension and dyslipidemia.

Management of hypertension in CKD is a critical issue, as blood pressure is often poorly controlled in early or advanced renal disease. Many factors contribute to the development of hypertension in CKD. Sympathetic overactivity plays an important role, apart from volume overload and increased renin-angiotensin activity. This review is an attempt to understand the significance of sympathetic activity in CKD and possible ways to address the same, with a focus on the role of α-blockers.

Causes and Consequences: Sympathetic Activity in Renal Disease

Causes of Increased Sympathetic Activity

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Fig. 1: Causes and Consequences of Sympathetic Activity in Renal Disease

Renal ischaemia is a very important causative factor, as the accumulation of adenosine triggers central sympathetic outflow. Increase in angiotensin II is another crucial mechanism, which may influence sympathetic activity via multiple mechanisms. Angiotensin II may act on the vasomotor centre in the brainstem, and may reset the blood pressure homoeostasis to a higher level. It may also act on the sympathetic nerve terminals, to increase the release and prevent the reuptake of norepinephrine. Stimulation of carotid chemoreceptors is also a likely mechanism, observable in dialytic patients due to the underlying mild acidaemia and nocturnal hypoxaemia. Reduction in nitric oxide availability and oxidative stress also result in increased sympathetic activity. Obesity may influence sympathetic activity through increased leptin and insulin levels. In patients with CKD, sympathetic activity induced by high serum leptin levels, contributes to the development of hypertension. Dyslipidaemia, observed commonly in CKD, may enhance the α-1 pressor sensitivity or impair the functioning of α-blockers.

Consequences

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of baroreceptor reflex. Sleep apnoea is frequently observed in association with dialysis. The resultant hypoxaemia also stimulates sympathetic activity. CKD is associated with reduced availability of nitric oxide (NO), owing to multiple factors prompting a decrease in NOS activity, increase in levels of natural inhibitors of NO such as asymmetric dimethyl L-arginine (ADMA), and oxidative stress. Such a state of reduced NO availability, enhances the hypertensive effect of sympathetic activity. Sympathetic overactivity may be genetically determined as well, with genes like phosducin playing important roles. Some or all of these mechanisms may jointly play a part, in the development of hypertension in patients with CKD.1-3 In patients on dialysis, hypertension is perceived to be largely volume dependent. However, the influence of sympathetic overactivity cannot be understated in these patients. Sympathetic activity contributes significantly to development of hypertension in renal disease.

**Consequences**

Sympathetic hyperactivity contributes to hypertension, and leads to significant damage to the kidneys and the cardiovascular system.1-5 In CKD, apart from the elevation in office BP, elevation in the ambulatory BP and lack of diurnal variation in BP are important clinical consequences. Ambulatory BP or circadian rhythm of BP are better predictors of clinical outcomes than office BP. Using these parameters, Cha et al demonstrated a significantly higher prevalence of masked and sustained hypertension in CKD patients.5 Masked or sustained hypertension is increasingly observed in proportion to the extent of kidney disease.5 Addressing the increased sympathetic activity assumes significant relevance, in the management of hypertension associated with renal disease.

Increase in blood pressure may result in glomerulosclerosis. This may be facilitated by podocyte injury mediated through adrenoceptors, independently of blood pressure. α-1 adrenoceptors are also involved in vascular smooth muscle proliferation, resulting in progression of atherosclerosis. Catecholamines can also influence inflammatory activity in the tissues. These adrenergic effects may contribute to kidney damage over a period of time, independently of blood pressure.1-3 In CKD, the availability of nitric oxide (NO) is reduced, which may increase the responsiveness to sympathetic activity. In such a state, even a low level of sympathetic activity may be detrimental to kidneys, on account of increased hypertensive and inflammatory actions.1-2

Non-clinical and clinical studies have demonstrated that inhibition of sympathetic activity slowed the progression of renal failure. Blockade of either of α or β adrenergic receptors, has demonstrated renal protection, with additive effects on combination.

Vonend et al observed that in patients with chronic renal failure (CRF) maintained on RAS inhibition, add-on central sympatheticlyctic moxonidine halted the progression of renal insufficiency, relative to CCB nitrendipine, with minimal influence on blood pressure.6 Moxonidine has also demonstrated reduction in albuminuria in early kidney disease, despite no change in ambulatory blood pressure.7 This highlights the importance of sympathetic activity in human kidney disease.

Apart from kidneys, increased sympathetic activity in renal disease, may significantly damage the cardiovascular system. Adverse cardiac outcomes include development of left ventricular hypertrophy, cardiac dysfunction, arrhythmias or failure. Vascular outcomes include increased arterial tone, vascular stiffness, and atherogenesis, which may result in complications. Alterations in haemostasis lead to increased coagulability. Even younger patients with renal disease may suffer from advanced coronary artery disease.1-4 Cardiovascular deaths account for substantial mortality in CKD patients.

**Role of α-Blockers**

In the Indian scenario, several drugs like clonidine and prazosin are commonly used, which are not represented in the international clinical guidelines of hypertension.7 Post the observations from ALLHAT, regarding increased risk of cardiac failure with doxazosin compared to chlorthalidone, the use of α-blockers as first line antihypertensive therapy has declined.8 However, in combination with other antihypertensives, α-blockers have demonstrated a good safety and efficacy profile as third line drugs.9-11 The good lipid and glycaemic profile of α-blockers also favour their utility in patients with these comorbidities, which are commonly observed with CKD. In the ASCOT trial, addition of doxazosin as the third antihypertensive drug resulted in improvements in BP control, without any increase in cardiac failure.9 Similar results were observed in a study by Ohta et al, which demonstrated the beneficial effects of addition of low dose doxazosin to RAS inhibitor and CCB combination regimens.10 The ZAFRA study, carried out in patients of chronic renal failure (CRF) with uncontrolled hypertension, evaluated the utility of α-blocker, as third add-on to RAS inhibitor and CCB.11 Over 6 months of follow-up, good antihypertensive effect was observed with the addition of α-blocker to antihypertensive regimen, without any observations of increased cardiac failure.11 These observations suggest a beneficial profile of α-blockers, when used as third line antihypertensive drugs, including in patients with renal failure.

Studies on α-blockers in patients with renal diseases, have consistently demonstrated beneficial effects in
terms of effective BP reduction, preservation of renal function and haemodynamics, and metabolic benefits. In a study on patients with CRF, doxazosin therapy resulted in effective BP control, along with increase in glomerular filtration and decrease in plasma BUN and creatinine levels. Reduction in BP was significantly correlated to reduction in proteinuria, over 6 months of doxazosin therapy. Metabolic benefits were also evident with doxazosin therapy, in terms of reduction in triglyceride levels and increase in HDL cholesterol levels. A study by Yildiz et al evaluated the effects of doxazosin on insulin resistance, in patients with CRF. Over 12 weeks of follow-up, insulin resistance (assessed by HOMA and fasting insulin levels) significantly decreased with doxazosin therapy. Another study by Erley et al evaluated the effects of various drugs (administered for 12 weeks) on renal function, in hypertensive patients with non-insulin dependent diabetes. Doxazosin therapy was associated with a significant improvement in creatinine clearance, which was more pronounced as compared to captopril therapy. Also, doxazosin therapy resulted in the reduction of proteinuria by 34%, an effect consistently observed in each diabetic patient studied.

Chronic therapy with prazosin has demonstrated a fall in renovascular resistance, with the afferent arteriole being the site of action, in principle. This observation implies consistent renal vasodilatation during chronic prazosin therapy, which facilitates preservation of renal function and renal blood flow, despite significant reduction of renal perfusion pressure. Prazosin has also demonstrated a marked decline in plasma renin activity, due to the complex interplay between RAS and adrenergic systems within the kidney. a1 adrenergic blockade may complement β adrenergic blockade in balancing the renal haemodynamic alterations, as is discussed in subsequent sections. a1 blockade is also associated with improvement in endothelial functioning. A study evaluated the effect of doxazosin, carvedilol and atenolol, on endothelial fibrinolytic activity and lipoprotein metabolism, in hypertensive patients with ischaemic heart disease. Doxazosin therapy was associated with an improvement in endothelial fibrinolytic activity (before or after anoxia), and beneficial modifications in lipoprotein ratio. Carvedilol administration improved endothelial fibrinolytic activity only after anoxia, and did not modify lipoprotein ratio. Atenolol did not improve fibrinolytic activity, and unfavourably modified lipoprotein ratio.

**Hypertension in Dialysis**

Hypertension is very commonly observed in ESRD patients, which results in cardiovascular morbidity and mortality. In patients on dialysis, various pathophysiological mechanisms lead to hypertension. Volume overload represents a very common problem in dialysis, which may also result in refractory hypertension. A resultant imbalance in RAS activity and ECF volume is frequently observed, leading to an increase in plasma renin activity. Increased sympathetic activity is an important feature, resulting from the fluctuating fluid volumes during dialysis, apart from the several other causative factors associated with kidney disease. Apart from volume, renin and sympathetic activity, other causative associations for hypertension in dialysis include erythropoietin replacement therapy, secondary hyperparathyroidism, nocturnal hypoxaemia and imbalance in endothelial vasoactive substances. Management of hypertension may pose significant clinical challenges for the dialysis patients.

Appropriate correction of volume overload is the most essential consideration, towards addressing the development of resistant hypertension. Pharmacotherapeutic approach during dialysis involves special considerations, as the kinetics of many drugs may be influenced by physiological changes. a1 blockers are largely bound to plasma proteins, and are relatively stable during dialysis. In a study by Vanholder et al, the protein binding capacity of prazosin fell by approximately ± 2% in dialysis. However, as prazosin is highly bound to plasma proteins (> 95%), even a modest increase in free drug concentration may have clinically relevant effects. Hence, careful titration of the dose may be necessary and lower doses of up to 3 to 8 mg / day may be effective. Good efficacy of prazosin has been observed in all types of hypertensive patients on dialysis, either as monotherapy or in combination, with minimal side effects. In patients with intradialytic hypotension, use of a blockers should be avoided.

**Hypertension in Renal Transplantation**

Cardiovascular risk is significantly associated with renal transplantation, and accounts for a huge mortality rate in these patients. Hypertension is widely observed post transplantation, and poses risk for renal allograft dysfunction, as well as for cardiovascular complications. For each 10 mmHg rise in systolic BP, the risk for allograft loss is increased by 12% to 15%. BP control is of prime relevance in transplant recipients. Hypertension may develop in transplant recipients due to multiple reasons. Apart from the causative factors observed in renal disease, dysfunction of the graft, or the use of immunosuppressant medications may contribute to high BP. Pre-glomerular vasoconstriction may be an essential factor in hypertension, rather than glomerular hypoperfusion.

In the pharmacological considerations...
for these patients, important considerations include renoprotection, favourable renovascular haemodynamics, minimisation of metabolic complications, and efficacy in patients receiving calcineurin inhibitors. α-blockers reduce peripheral resistance, preserve and may improve renal haemodynamics, and preserve renal function.19,24-27 Their use is associated with favourable metabolic profile and minimal risk of hyperkalaemia. α-blockers have also demonstrated good efficacy in patients receiving cyclosporine. These characteristics make α-blockers preferable agents in renal transplant recipients.24-27

A study compared the profiles of doxazosin and enalapril monotherapies in a cross-over design, in transplant recipients receiving cyclosporine. A similar BP control was observed in both the groups, but doxazosin was associated with better profile in terms of renal function, potassium level, or haemoglobin.27 Prazosin therapy has demonstrated good efficacy and tolerability profile, along with preservation of renal function.26 Patients may respond to relatively smaller doses of these drugs, and initiation of therapy with lower doses, with gradual titration, should be the preferred approach.

A long term study over 3 years, evaluated the antihypertensive profile of doxazosin, enalapril and verapamil in renal transplant recipients.24 In long term, 8 patients in each of the verapamil or enalapril groups, compared to only 4 patients in doxazosin group, lost the graft due to chronic transplant nephropathy. Initial tolerance to verapamil was poor, whereas enalapril use was associated with long term hyperkalaemia and coughing. Doxazosin was very well tolerated, and relative hypotension was observed in only 2 patients.24 First dose hypotension may be a concern, particularly with the older standard formulations of α-blockers. This can be minimised with the use of slow and sustained release formulations.

**Combining α and β Blockers**

Combination of α and β blockers is a rational approach, for more effective and complete control of the increased sympathetic activity. Apart from the synergistic mechanisms of these two drug classes, additional safety advantages may be expected, particularly with regards to β-blocker use. α-blockers are associated with good antihypertensive efficacy, metabolic benefits, favourable renal haemodynamics and reduction in risk of hyperkalaemia. While β-blockers offer less than adequate efficacy in lowering BP and in vascular protection, most of these agents are associated with poor metabolic profile, hyperkalaemia or unfavourable renal haemodynamics.28-30 In absence of cardiac disease, β blockers are not the preferred antihypertensive agents. However, in chronic kidney disease associated with cardiac failure or dilated cardiomyopathy, the use of β blockers has demonstrated reduction in cardiovascular risk.31-33 In CKD patients without pre-existing cardiac comorbidities, the extrapolation of these cardiac benefits of β blockers is not proven.30-32

Various β-blockers differ in their receptor blocking, pharmacologic and adjunctive properties, and have variable effects on renal haemodynamics. The older nonselective agents, the cardioselective agents, and newer agents with vasodilating properties, demonstrate markedly differing clinical profiles. Their respective combinations with α blockers may have differing implications for clinical use.

Nonselective β-blockers reduce the GFR and renal blood flow, excepting the agents with vasodilatory effects. Labetolol has demonstrated conflicting evidence on renal haemodynamic alterations.30 Nonselective β-blockers like propranolol may cause a reflex increase in sympathetich activity, owing to reduction in cardiac output and blockade of β2 mediated vasodilation. This results in unopposed α1 activity, and unfavourable renal haemodynamics. Chronic administration of these agents could potentially exacerbate renal dysfunction.30 A study compared the effects of prazosin and propranolol, on renal perfusion changes in essential hypertension.34 Following 1 month of therapy, prazosin, but not propranolol, was associated with preservation of glomerular filtration rate, renal plasma flow, and renal blood flow. Addition of α1 blockade may thus effectively counter the reflex vasoconstriction, and may increase blood flow to skeletal muscle, thereby benefitting the glycaemic profile.34 Nonselective β-blockers may also cause hyperkalaemia in ESRD patients, and in patients taking mineralocorticoid antagonists. α1 blockade may be protective against this adverse effect, and may also facilitate sodium excretion.30

Cardioselective β1-blockers may preserve renal haemodynamics, and have been used successfully in CKD patients. However, like the nonselective agents, cardioselective agents may also result in insulin resistance and worsening lipid profile, including increased triglyceride and decreased HDL cholesterol levels. Addition of α1-blocker can effectively negate these adverse metabolic effects of β-blockers, by improving insulin sensitivity, lowering triglyceride and increasing HDL cholesterol levels. Hence, combination of α1 and β1 blockade may benefit diabetes as well as atherosclerotic vascular disease.30

The newer β blockers with vasodilating properties may be particularly recommended for patients with pre-existing cardiac comorbidities, including coronary artery disease and heart failure. A study evaluated the efficacy of carvedilol in patients undergoing haemodialysis, and with coexistent
dilated cardiomyopathy. In this study, the use of carvedilol was associated with significant reduction in morbidity and mortality over 2 years, suggesting its possible benefits in dialysis patients with chronic heart failure. A meta-analysis suggested possible benefits of carvedilol in heart failure, in patients with early, but not advanced CKD. However, in terms of antihypertensive efficacy, vascular protection and metabolic advantages, evidence of superiority relative to α blockers is lacking. A study compared add-on doxazosin or carvedilol, in hypertensive patients with mild heart failure, receiving enalapril and furosemide. Doxazosin, in combination therapy, rapidly improved clinical status and haemodynamics, by reduction of afterload. Persistent superior benefits were observed with doxazosin compared to carvedilol, in terms of BP reduction, at 3 weeks and at 12 months. Ejection fraction, exercise tolerance and quality of life significantly improved with doxazosin compared to carvedilol in the initial 3 weeks; the differences in these parameters were not significant at 12 months. A significant improvement in lipid profile was observed with doxazosin at 3 months, compared to carvedilol. In a study in hypertensive patients with ischaemic heart disease, doxazosin therapy demonstrated superior improvement in endothelial fibrinolytic activity and lipoprotein metabolism compared to carvedilol and atenolol.

These observations collectively suggest that α-blockers are important components in combination antihypertensive therapy, owing to their superior benefits in terms of BP control and metabolic advantages. Combination of α and β blockers may result in synergistic antihypertensive benefits, possible reduction in cardiovascular risk, and limitation of adverse effects. In the ASCOT trial, 11,768 patients were administered doxazosin as a third line therapy. In patients who were concomitantly receiving atenolol, reductions in systolic and diastolic BP were more pronounced on addition of doxazosin, as compared to patients not receiving β blocker based regimen. Combination of these two antihypertensive drug classes, may thus be a rational approach in patients with renal disease.

**Conclusion**

Increased sympathetic activity is an important feature in renal disease, which significantly contributes to development of hypertension and to target organ damage. α blockers have an essential place in the management of hypertension in renal disease, owing to their good antihypertensive efficacy, favourable metabolic profile, excellent tolerability particularly with modified formulations, need for minimal dose adjustments during dialysis, and suitable profile for transplant recipients. Studies have confirmed the utility of α blockers as effective and safe add-on drugs in antihypertensive regimens. Combination of α and β blockers may also be a rational approach in renal disease.

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