Review

Drug management of hypertension in hemodialysis patients

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Abstract: Hypertension is believed to be a major risk factor that causes cardiovascular disease in patients on hemodialysis (HD). Removing of excess water during HD, accurate assessment of dry weight and anti-hypertension therapeutics are the most commonly used measures to lower blood pressure in patients on HD.
Keywords: Hypertension; Hemodialysis; End-stage renal disease

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Contents

1. Introduction

Hypertension is a common complication in end-stage renal failure patients undergoing hemodialysis (HD). A clinical trial has reported[1] that pre-dialysis systolic blood pressure (BP) in 70% of the patients was higher than 140 mmHg, despite 75% patients of those objects have undergone antihypertensive therapy. The causes of hypertension in hemodialysis patients are multifactorial, and the mechanism is quite complicated. Excess water, hyperactivity of renin-angiotensin system, sympathetic hyperactivity, impaired endothelial cell-mediated vasodilatation, an increase in circulating natriuretic peptides, correction of anemia with erythropoietin secondary hyperparathyroidism and arteriosclerosis are the factors that we have already known. In particular, inaccurate assessment of dry weight contributes to the water overload in patients on HD and cardiovascular disease.

The kidneys play a vital role in the regulation of water balance by excreting excess sodium and water. In the patients with renal failure, sodium and water is prone to overload because of the kidneys are disable to excrete excess sodium and water. Retention of excess water expands the plasma volume and raises the peripheral resistance, further more, raises the blood pressure[2,3]. It has been documented that the incidence of hypertension in the patients with renal failure is higher than the patients with normal renal function[4]. Dialysis is an effective tool for the removal of excess water. However, more than 30 years after the commencement of dialysis therapy, majority of patients on hemodialysis remains hypertensive[5]. Long-term hypertension is closely

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related to increasing mortality in the patients with renal failure[6,7]. The purpose of this article is to review the literatures concerning hypertension in hemodialysis patients and emulate several effective methods on controlling hypertension in hemodialysis patients.

2. Methods of managing hypertension in hemodialysis patients

2.1. Individualized dialysate sodium concentration

Hemodialysis can reduce blood pressure in patients with renal failure by removing excess water and sodium based on the patients strictly restrict dietary water and sodium intake, otherwise, salt and water retention would be recurred, as a result of that, blood pressure will be out of control. In order to evaluate this hypothesis, Dr. de Paula conducted a clinical trial with 27 non-diabetic, non-hypertension prone hemodialysis patients[8]. At the beginning, patients underwent nine consecutive HD sessions with the dialysate Na^+ concentration at 138 mEq/L (standard dialysate Na^+), after that, they were treated with nine sessions with individualizing dialysate Na^+ concentration. In the second phase, the dialysate Na^+ concentration was individualized based on the plasma Na^+ level before hemodialysis, and the Na^+ level was calculated by three times of the patient's average pre-hemodialysis plasma Na^+ and multiplied by 0.95. The result showed there was a significant decrease in inter-dialytic weight gain, inter-dialytic thirst scores, and dialysis related hypotension and related symptoms in the second phase. Pre-HD blood pressure was reduced remarkably in patients with uncontrolled BP at baseline in the second phase, too. The result suggested that individualizing sodium prescription is more effective in controlling hypertension in hemodialysis patients.

2.2. Accurate assessment of dry weight and a reasonable dialysis program

Accurately assessing dry weight in hemodialysis patients during dialysis contributes to the control of hypertension and prevention of dialysis related symptoms. Dry weight is the ideal body weight at the end of a dialysis session. There are several definitions of dry weight. Mailoux and Haley define it as the weight at which the patient can remain normotensive until the next dialysis session without the use of antihypertensive medications[5]. Dry weight cannot be assessed in a single parameter, and a consummate clinical assessment should take into account the following parameters, including pre-dialysis BP and weight, pre-tibial edema, chest auscultation for signs of pulmonary edema, and assessment of jugular venous pressure[9,10]. Besides, the patient's inter-dialytic well-being, episodes of intra-dialysis side effects and recent use of anti-hypertensive can also be assessed[11]. Dry weight assessment needs to be reapplied regularly, at least once every two weeks, to ensure each patient's target post-dialysis weight reflects his real dry weight[12]. In addition to the clinical assessment, bioelectrical impedance analysis (BIA) has been widely applied[13]. BIA can estimate fluid status. When symptom of dehydration and hypertension coexist in patients, BIA could help us to judge whether there is extracellular fluid overload or not. Extrapolation of patient's biochemistry results, measurement of the inferior venal caval diameter and consecutive blood volume monitoring are also used for assessing dry weight. However, each of the methods has its own deficient. Currently, clinical assessment is still a basic and effective way to assess hydration status. Carefully observing and recording patient's clinical symptoms is important for formulating a reasonable dialysis program in order to control the hypertension in hemodialysis patients.

2.3. Dialysis with a low calcium dialysate

Dialysis with a low calcium dialysate is an effective way to achieve normal BP to the patients who fail to control hypertension after achieving target dry weight. Dr. Faissal Tarrass performed a clinical trial to demonstrate his hypothesis[14]. Total of 168 end-stage renal failure patients, who have been on maintenance HD for at least six months, were selected in this study. Patients having pre-dialysis blood pressure of more than 140/80 mmHg, with or without edema,

and those who required antihypertensive medication to control blood pressure were identified as hypertensive. First, patients reach the optimal dry weight by dialyzing with a 1.75 mEq/L calcium dialysate. After reduction of dry weight, patients with uncontrolled arterial hypertension were dialyzed using a 1.25 mEq/L calcium dialysate. As a consequence, the number of patients with good control of predialysis BP in the first data collection is 40 patients (80%), and the number in the second phase is 45 patients (90%). The average blood pressure of the controlled groups in the second phase was lower than the first phase. Another study[14] reported that in the patients with normal cardiac function, low calcium dialysate leads to a significantly decline in blood pressure during dialysis compared with high dialysate calcium concentration. It is supposed that[15] alteration in dialysate calcium concentration within the physiological range could affect blood pressure primarily through changes in left ventricular output rather than in peripheral vascular.

2.4. Reasonable use of antihypertensive medications

Conventional hemodialysis combined with antihypertensive medications is beneficial for majority dialysis patients. Several classes of antihypertensive drugs are available, such as, calcium channel blockers (CCBs), β-blockers, angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), direct vasodilators and centrally acting sympathetic agonists. For making a reasonable choice of antihypertensive drugs, we should take both patient's condition and pharmacokinetics of drugs into consideration.

2.4.1. Calcium channel blockers

CCBs are the most widely prescribed class of drugs in patients on hemodialysis, recently. It can effectively lower blood pressure and improve the status of volume overload in hemodialysis patients, and it associates with a lower risk of total cardiovascular mortality as well[16,17]. This finding is particularly notable for patients with the history of cardiovascular disease[17]. Besides, patients with end-stage renal disease (ESRD) used to have excessive oxidative stress and elevated plasma levels of oxidation products of lipids, thiols, proteins, nucleic acids, asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA). Evidences suggest these substances are associated with dyslipidemias and cardiovascular disease (CVD) in hemodialysis patients, ADMA supposed to be an independent predictor of endothelial dysfunction and CVD in both patients with ESRD and healthy population. In a study of antihypertensive treatment with amlodipine (CCB) and valsartan (ARB) for 6 weeks, researchers found that both amlodipine and valsartan can lower the plasma levels of oxidative stress products and the ADMA in patients with ESRD on HD, and amlodipine was more effective than valsartan[18]. Yet, this research did not document the outcome of these patients on HD.

In general, the volume of distribution (Vd), protein binding and plasma half-life of CCBs are comparable in ESRD patients, non-ESRD renal failure patients, and normal renal function subjects, with a few notable exceptions. One such exception is nicardipine where plasma clearance is decreased in chronic renal failure patients when compared with normal subjects. However, it is corrected by hemodialysis. Besides, the dialysance of these drugs is uniformly low because of their high protein binding and large Vd[19]. Therefore, dose adjustment and post-dialysis supplement are not required in hemodialysis patients.

2.4.2. β-Blockers

There has been an association between β-blockers use and lower mortality in hemodialysis patients, particularly those without the history of heart failure[20,21]. Besides, β-blockers have significant effects in patients with acute coronary syndrome, and a number of studies showed highly significant associations between treatment with β-blockers and sudden cardiac death in patients on HD. Patients treated with β-blockers have a low rate of sudden death and ventricular arrythmias[22,23]. It was reported this phenomenon is related with sympathetic over activity caused by hemodialysis, as increased sympathetic activity is a well known risk factor for sudden death[24]. β-Blockers can be divided into two

major categories, hydrophilic agents and lipophilic agents. Hydrophilic agents, such as atenolol, which is particularly valuable for noncompliant hemodialysis patients[25], are excreted primarily by the kidneys and require dose adjustment in patients with ESRD. Besides, it is easy to be eliminated by dialysis and requires supplementation to avoid exacerbation of arrhythmias following dialysis. Lipophilic agents is metabolized primarily by the hepatic and with little being excreted unchanged in the urine. In addition, dialysis would not eliminate lipophilic agents and post-dialysis supplementation is not required, with a few notable exceptions. One such exception is metoprolol, it can be eliminated by dialysis and thus a supplementation is needed[20,26].

2.4.3. Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers

ACEIs are attractive in the therapy of dialysis patients by interfering with the renin-angiotensin-aldosterone system. Several antihypertensive agents have no side effects on plasma glucose levels. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) suggests ACEIs are the preferred antihypertensive agents in hemodialysis patients, particularly those with diabetes mellitus or a history of heart failure[26]. Parts of ESRD patients in hypervolemia status have low levels of circulating renin, for these patients, high values of their plasma Na^+ concentration will interfere the effect of ACEIs, even the dialysate Na^+ concentration. A study has showed that saline solution infusion could change the lowered blood pressure values after the administration of ACEIs[27].

Renal insufficiency is associated with reduced elimination of most ACEIs and altered pharmacokinetic properties, particularly in patients with GFR<30 to 40 mL/min. Most of the ACEIs (except for fosinopril) are removed with hemodialysis. Kidney eliminations of ACEI are illustrated in the Table 1[28]. For the drugs are mostly eliminated by hemodialysis require a supplement after dialysis. Fosinopril is primarily eliminated through the renal and hepatic routes. Further, with a high plasma protein binding, fosinopril is poorly eliminated by dialysis, dose modifications are not necessary in patients with renal dysfunction[29].

Table 1. Kidney eliminations of ACEIs

ACEIs	Normal $t_{1/2}$ (h)	$t_{1/2}$ in ESRD	Removal rate with hemodialysis (%)
Fosinopril	12	Prolonged	<10
Captopril	2	20–30 h	100
Benazepril	11	Prolonged	20–50
Enalapril	11	Prolonged	35
Lisinopril	12	54 h	50
Ramipril	13–17	Prolonged	<30

ARBs have similar effects to ACEIs in hemodialysis patients. It is generally well tolerated and has fewer side effects than ACEIs. There is a study[30] evidence that an ARB, combined with another antihypertensive medication (not an ACEI), may be more effective than an ACEI and non-ARB antihypertensive medicine therapy on cardiovascular mortality in patients on HD. However, combination ACEI and ARB therapy is detrimental for hemodialysis patients compared with mono-therapies with ACEIs or ARBs. For this phenomenon, someone speculate that effects of reactive renin and prorenin release on the prorenin receptor (PRR) may be a reasonable explanation[31]. As the renin-angiotensin system is blocked by ACEIs and ARBs, renin binds to PRR and its catalytic activity increases, contributing to highly efficient generation and activity of AT II. Meanwhile, prorenin attains a high plasma level and binds to PRR with greater affinity than renin, thus can contribute to local Ang II formation[31,32]. Aliskiren, a direct renin inhibitor (DRI), provides the most comprehensive inhibition of the Renin-angiotensin-aldosterone system (RAAS), reducing plasma renin activity. It's more effective in lowering blood pressure compared with ACEIs and ARBs[33]. Moreover, aliskiren can counteract the overactivity of plasma renin induced by ACEIs and ARBs, decrease the PRR gene and block the activity of prorenin[31,32]. In conclusion, DRIs may improve the combination ACEI and ARB therapy in patients on HD.

The predominant elimination pathway of ARBs is hepatic route and these agents with typically high protein binding, as a result it is poorly dialyzed and a post-dialysis supplement is unnecessary[34]. It is notable that, both ACEIs and ARBs can cause anemia in hemodialysis patients, the mechanisms for this phenomenon are still in question.

2.4.4. Diuretics

Diuretic is a traditional antihypertensive agent. However, the role of diuretics in the management of hemodialysis patients has not been clearly defined. The use of diuretics is often discontinued after starting dialysis therapy, because it supposed to be no longer effective as patients need hemodialysis therapy. Currently, there is a hypothesis saying that diuretics can protect residual renal function and reduce mortality in patients on hemodialysis. Bragg-Gresham's study confirmed this hypothesis[35]. The result showed a significant decrease in inter-dialytic weight gain, dialysis related hypotension and mortality in hemodialysis patients, whether with residual renal function or not. But more clinical trials are needed for demonstrating this hypothesis.

Antihypertensive drugs can be either used alone or combined in the management of hypertension, a single drug is difficult to control blood pressure completely. ESH/ESC guidelines (2009) for hypertension suggested that most patients require a combination of two kinds of drugs at least. For clinical refractory hypertension, combination therapy should be considered. In addition, drugs compatibility should be considered carefully to prevent adverse consequences, for example, the combination of β-blockers with verapamil or diltiazem would cause atrioventricular blockade.

3. Summary

All of these approaches can control hypertension in hemodialysis patients effectively. However, there are some patients still with hypertension. This phenomenon may be caused by genetic polymorphisms or other causes that we have ever known, and then a further investigation is needed.

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血液透析患者的高血压药物控制

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摘要: 高血压是血液透析患者心、脑血管并发症的重要危险因素。清除体内过量水分, 准确评估患者干体重, 抗高血压药物治疗是目前比较常用的有效控制透析患者高血压、降低心血管事件发生率和病死率的治疗手段。

关键词: 高血压; 血液透析; 终末期肾病

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