Review

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Pharmacologic Management of the Cardio-renal Syndrome

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Cardio-renal syndromes are disorders of the heart and kidney wherein acute or long-term dysfunction in one organ may induce acute or long-term dysfunction of the other. Because of this complex organ interaction, management of cardio-renal syndrome must be tailored to the underlying pathophysiology. Clinical guidelines exist for the treatment of heart failure or renal failure as separate conditions. Thus far, however, there has been no consensus about managing patients with cardio-renal and reno-cardiac syndromes. Pharmacologic treatment remains a controversial subject. Standard cardiac drugs such as diuretics and inotropes may have limited effect because resistance often develops after long- term use. Recent studies of patients with acute cardio-renal syndromes have focused on newer therapies, including phosphodiesterase inhibitors, vasopressin antagonists, adenosine A1 receptor antagonists, and renal protective dopamine. Initial clinical trials of these agents have shown encouraging results in some patients with heart failure, but have failed to demonstrate a clear superiority over more conventional treatments. Similarly, the benefits of diuretics, aspirin, erythropoietin agents, and iron supplements for management of chronic cardiorenal syndromes are unknown.

Key Words: Cardio-renal syndrome; Management; Drug

Introduction

Cardiac dysfunction often precedes a decrease in kidney function and progression of kidney disease[1]. Conversely, renal dysfunction is one of the most important co-morbidities in heart failure, and is a potent predictor of cardiovascular complications and mortality[2]. The codependent relationship between heart and kidney failure is commonly termed cardio-renal syndrome (CRS). Recently, a new definition and classification of CRS has been proposed to increase understanding of this syndrome and its underlying mechanisms[3].

Cardiac and renal dysfunctions share similar pathophysiology, and this may explain why they often occur simultaneously. Proposed mediators of this connection include activation of the renin-angiotensin-aldosterone system (RAAS), imbalance between nitric oxide and reactive oxygen species, the sympathetic nervous system, and inflammation[4].

Although clinical guidelines exist for managing acute and chronic heart failure and renal dysfunction independently, there is no consensus on managing patients with cardio-renal and/or reno-cardiac syndrome[5]. Most clinical studies of heart failure predominantly recruited patients whose kidney function were relatively normal[6]. Because there have been no trials specifically in populations with concomitant cardiac and renal dysfunction, the efficacy and safety of CRS therapies cannot be assessed and evidence-based treatment recommendations cannot be made. Thus, the pharmacologic management of patients with CRS remains a huge challenge.

However, recently, novel treatment options have been investigated for protecting or improving heart and kidney

function. Moreover, due to the increasing incidence and importance of CRS in the present clinical setting, existing treatments are also being modified to provide more beneficial effects for heart and kidney function than previously provided by conventional treatments. The International Acute Dialysis Quality Initiative Panel recently published a comprehensive consensus statement about CRS, including management strategies[5]. The purpose of this article is to review therapeutic pharmacologic alternatives for the management of patients with concomitant heart and kidney failure, to discuss their potential impact on clinical outcomes, and to highlight areas for future research.

Management of Acute Cardio-renal Syndrome

In acute CRS, specific treatment is designed to ameliorate decreased urine output, decreased glomerular filtration rate, increased serum creatinine, and to prevent weight loss. Current pharmacologic management consists of inotropic agents and vasodilators in the majority of cases, and also includes neurohormonal antagonists and diuretics. Drugs targeting the kidney, such as vasopressin antagonists, adenosine antagonists, and natriuretic peptides, have potentially therapeutic value, although to date, the results of clinical studies using these treatments have been disappointing.

Inotropic Agents and Low-dose Dopamine

Inotropic agents are widely used to treat patients with low blood pressure and poor cardiac output. Drugs such as dobutamine and milrinone improve cardiac index in proportion with renal blood flow, but these improvements are not clearly associated with better clinical outcome or reduced mortality.

The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of a Chronic Heart Failure (OPTIME-HF) trial reported that milrinone did not improve kidney function or overall survival in acute decompensated heart failure (ADHF) patients[7]. Low-dose dopamine (<5 μg·min-1·kg-1), commonly combined with diuretics, is believed to increase renal vasodilatation and renal blood flow, attenuate the effects of norepinephrine and aldosterone, and promote natriuresis via effects on dopamine-1 and 2 receptors[8]. A prospective, double-blind, randomized, controlled study concluded that low-dose dopamine can worsen renal perfusion in patients with acute renal failure, supporting a trend to abandon the routine use of low-dose dopamine in critically ill patients[9]. However, other studies challenge this conclusion. The Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial found that the combination of low-dose furosemide and low-dose dopamine is equally effective as high-dose furosemide and is also associated with improved renal function and potassium homeostasis[10]. Therefore, treatment with low-dose dopamine could be useful for CRS patients who require high-dose furosemide. A small randomized trial of levosimendan, a calcium sensitizing phosphodiesterase inhibitor, involving patients with heart failure showed an increase of 45.5% in estimated glomerular filtration rate (GFR) at 72 hours in the levosimendan group versus 0.1% GFR increase in those treated with dobutamine[10]. Although these results are promising, other clinical studies do not seem to support them. The Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study showed that levosimendan did not significantly reduce all-cause mortality or affect any secondary clinical outcomes, and the value of this drug for treatment or prevention of CRS remains unclear[11].

Diuretics and Vasodilators

Diuretics and vasodilators play an important role in the early management of CRS and its complications of venous hypertension, increased intra-abdominal pressure, and renal congestion[12]; they also provide short-term symptomatic relief to CRS patients. However, in high doses, diuretics may aggravate electrolyte disturbances, decrease the effective circulating volume, disturb neurohormonal balance, and lead to decreased kidney function. Since both

heart failure and renal dysfunction frequently require high-dose diuretic treatment, the administered dose must be carefully calculated to improve fluid balance and relieve symptoms without stimulating adverse physiologic effects.

Vasodilators can rapidly decrease ventricular filling pressures and central venous pressure, thereby reducing myocardial oxygen consumption and relieving pulmonary congestion. Intravenous nitroglycerine, a vasodilator commonly used to treat ADHF, may also reduce trans-renal perfusion pressure by decreasing venous pressure[13]. However, it is not clear whether the effect of nitroglycerine improved kidney function or long-term survival. Sodium nitroprusside produces significant arterial and venous vasodilatation through its action on cyclic guanosine monophosphate in vascular smooth muscle. In a nonrandomized trial, ADHF patients treated with sodium nitroprusside experienced favorable long-term clinical outcomes irrespective of inotropic support or kidney dysfunction[14]. However, thiocyanate accumulation is a dangerous potential side effect in patients with decreased kidney function.

Nesiritide, a recombinant form of human B-type natriuretic peptide, produces venous, arterial, and coronary vasodilatation, decreasing the cardiac preload and afterload and increasing cardiac output without direct inotropic effects. Investigations involving the safety and physiologic effects of nesiritide show mixed results. In one study of ADHF patients, nesiritide significantly increased the risk of worsening renal function, even at low doses ($\leq$0.015 μg·kg-1·min-1)[15]. Nevertheless, subsequent studies suggested that this drug could still potentially be used in renal-protective therapy in ADHF, with appropriate doses (0.01 μg·kg-1·min-1)[16,17]. The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) showed that nesiritide was not associated with a change in the rate of death and re-hospitalization, and had no unfavorable effects on kidney function compared with a placebo. Although nesiritide may not be recommended for routine use in most patients with acute heart failure, it could be used for short-term treatment in patients resistant to commonly prescribed drugs such as diuretics and vasodilators[18].

Vasopressin and Adenosine Antagonists

Selective vasopressin V2 antagonists, such as tolvaptan and conivaptan, can facilitate free water clearance, and increase the serum sodium level without disturbing plasma potassium and magnesium levels[19]. The Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial investigated 4,133 patients with ADHF and found that early administration of tolvaptan was associated with decreased mean body weight and improved dyspnea. Although comparison of tolvaptan and placebo groups showed no difference in long-term outcomes[20], vasopressin antagonists could relieve symptoms in selected patients with hyponatremia and oliguria. Increased adenosine levels in heart failure may exacerbate renal dysfunction. Drugs that selectively block adenosine A1-receptors and preserve adenosine A2-receptor activity can increase urine output while maintaining kidney function. In one study, patients who received rolofylline, a selective A1 receptor antagonist, showed a persistent increase in urine output without a decline in kidney function[21]. However, the PROTECT trial[22] failed to demonstrate any functional benefit or improvement in outcome including death or re-hospitalization for cardiovascular or renal disease. Similarly, the REACH-UP trial-a multicenter, international, randomized, double-blind, placebo-controlled study of patients with ADHF-showed no clear beneficial effect of rolofylline on the clinical status and recent or acute worsening of renal function[23]. In conclusion, the efficacy of adenosine A1-receptor antagonists for treatment of CRS is still undecided and larger clinical trials are needed to resolve this issue.

Management of Chronic Cardio-renal Syndrome

RAAS blockade

RAAS inhibitors have been shown to reduce mortality

in patients with cardiac failure, although the majority of these studies excluded patients with significant renal impairment[6]. In addition to improving survival in heart failure patients, these drugs also prevent progression of renal insufficiency in diabetic nephropathy and other forms of chronic kidney disease. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)[24] of patients with severe heart failure included individuals with renal dysfunction whose serum creatinine concentrations did not exceed 3.4 mg/dL. The subgroup of patients with serum creatinine levels higher than 2 mg/dL exhibited an improvement in outcomes when treated with an angiotensin-converting enzyme (ACE) inhibitor. The ACE inhibitors or angiotensin II-receptor blockers (ARB) should be used cautiously in patients with CRS, considering the associated risks of hyperkalemia and transient increase in creatinine levels. The patients should be started on the lowest dose of RAAS blockers and kidney function should be closely monitored during initiation and up-titration in order to reduce the incidence of renal deterioration; this is especially important for dehydrated patients. Moreover, concomitant use of NSAIDs should be avoided[6].

Spironolactone and eplerenone decrease morbidity and mortality in patients who develop heart failure after acute myocardial infarction. The RALES and EPHESUS trials[25-26] demonstrated that, in patients already receiving standard medications for heart failure, adding low-dose spironolactone or eplerenone dramatically improved the outcome. Although several studies confirm that mineralocorticoid receptor antagonists have organ protective effects, patients with renal dysfunction are at greater risk of hyperkalemia. Thus, the long-term effects of mineralocorticoid receptor antagonists on renal outcome, mortality, and safety in patients with CRS requires further study.

β-blockers

Activation of the sympathetic nervous system is a common occurrence in cardiac and renal failure. Interrupting this response is important to preventing progression of cardiovascular and renal disease. The β-blocker carvedilol has favorable effects on renal function in select patients with heart and kidney disease, and may offer a benefit over older formulations of β-blockers[27]. However, large randomized clinical trials on β-blocker treatment in heart failure excluded patients with severe renal dysfunction and did not consider their effects on renal outcome.

Antithrombotic therapy

Although aspirin can potentially interfere with GFR through its actions on cyclooxygenase and renal prostaglandins, aspirin in low doses has long been considered safe for use in patients with kidney disease. This was confirmed in the first UK Heart and Renal Protection Study[28], which showed that low-dose aspirin (100 mg/d) did not significantly impair kidney function or increase the risk for renal replacement therapy, nor did it substantially increase the risk for major bleeding even in patients with risk factors for minor bleeding. The efficacy of other antithrombotic agents, such as clopidogrel and low-molecular weight heparins, in patients with decreased renal function is uncertain and needs further investigation[29,30].

Anemia management

Anemia is present in over one-third of CRS patients[31]. Cardio-renal anemia syndrome (CRAS) refers to the simultaneous presence of anemia, heart failure, and renal failure, forming a pathologic triad that adversely impacts morbidity and mortality[32]. There is no consensus over the definition, significance, and management of CRAS. The role of erythropoiesis-stimulation agents (ESAs) in the treatment of CRAS is particularly controversial. Elevated serum erythropoietin is an adverse predictor of morbidity and mortality in heart failure[33,34]. However, erythropoietin receptor activation in the heart may be protective for apoptosis, fibrosis, and inflammation, providing a rationale for using ESAs in patients with heart failure[35]. A randomized double-blind controlled study showed that the correction of anemia with erythropoietin and oral

iron over 1 year led to improvements in cardiac function, left ventricular remodeling, and B-type natriuretic peptide levels compared with oral iron therapy alone[36]. There is also increasing interest in the use of parenteral iron to correct anemia in patients with congestive heart failure. Two recent trials, FERRIC-HF and FAIR-HF[37,38], demonstrated that patients treated with intravenous iron showed symptomatic improvement and increased exercise capacity independent of the effects on hemoglobin level. This data suggests that intravenous iron therapy is a potential option for the treatment of CRAS.

Conclusion

This review provided an overview of the current pharmacologic treatments for acute and chronic CRS and discussed the rationale for their use. Appropriate management strategies in CRS remain the subject of controversy. A multidisciplinary approach to the study and treatment of CRS and a deeper understanding of its pathophysiology are required to improve clinical outcomes.

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