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MODULATORY EFFECTS OF EPLERENONE ON NEUROHUMORAL BALANCE AND RENAL FUNCTION IN CARDIORENAL SYNDROME: A PROSPECTIVE STUDY

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Abstract: Cardiorenal syndrome (CRS) represents a complex interaction between cardiac and renal dysfunction, significantly worsening clinical outcomes in patients with chronic heart failure (CHF). Neurohumoral activation, particularly involving the renin–angiotensin–aldosterone system (RAAS), plays a central role in disease progression.

The aim of this study was to evaluate the effects of eplerenone-based therapy on neurohumoral markers and renal function in patients with CRS associated with CHF (NYHA class II–III).

A prospective controlled study included 115 patients diagnosed with CRS. Patients were divided into two groups: standard therapy (n=57) and standard therapy plus eplerenone (n=58). Serum levels of kallikrein, NT-proBNP, and aldosterone were measured before and after 12 weeks of treatment. Renal function was assessed using cystatin C–based estimation of glomerular filtration rate (GFR). Statistical analysis was performed using Student's t-test and Pearson correlation analysis.

Eplerenone therapy resulted in significant improvement in neurohumoral parameters. Kallikrein levels increased from 443 ng/ml to 781 ng/ml ($p<0.001$), while NT-proBNP and aldosterone levels significantly decreased ($p<0.05$). Additionally, GFR showed a significant improvement in the eplerenone group. Clinical symptoms, including dyspnea and exercise tolerance, also improved.

In conclusion, eplerenone therapy contributes to the modulation of neurohumoral balance in CRS by suppressing aldosterone activity and indirectly activating the kallikrein–kinin system, leading to improved renal function. These findings support the use of eplerenone in the early stages of cardiorenal syndrome.

Keywords: cardiorenal syndrome, eplerenone, mineralocorticoid receptor antagonist, neurohumoral modulation, aldosterone, NT-proBNP, kallikrein–kinin system, cystatin C, glomerular filtration rate, chronic heart failure

Introduction

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Chronic heart failure (CHF) remains one of the leading causes of morbidity and mortality worldwide, posing a significant burden on healthcare systems [1,4,19]. Despite advances in pharmacological therapy, the prognosis of CHF patients remains unfavorable, particularly in the presence of comorbid conditions such as renal dysfunction. It is estimated that more than 50% of patients with CHF develop varying degrees of renal impairment, leading to the development of cardiorenal syndrome (CRS) [2,12].

Cardiorenal syndrome is characterized by a complex and bidirectional interaction between the heart and kidneys, where dysfunction of one organ contributes to the deterioration of the other. The pathophysiology of CRS is multifactorial and involves not only hemodynamic disturbances but also activation of neurohumoral systems [3,10]. Among these, excessive activation of the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system plays a pivotal role in disease progression [6,11].

Aldosterone, a key effector of RAAS, contributes to sodium and water retention, myocardial and renal fibrosis, and endothelial dysfunction, thereby exacerbating both cardiac and renal injury [5,15]. Persistent neurohumoral activation leads to structural and functional remodeling, accelerating the progression of CHF and CRS.

In contrast, the kallikrein–kinin system exerts protective effects through vasodilation, natriuresis, and anti-fibrotic mechanisms, acting as a counter-regulatory pathway to RAAS activation [6,8]. Therefore, the imbalance between harmful and protective neurohumoral pathways plays a crucial role in the pathogenesis of CRS.

Recent therapeutic strategies for CHF and CRS emphasize a comprehensive approach, including angiotensin receptor–neprilysin inhibitors (ARNI), sodium-glucose cotransporter-2 (SGLT2) inhibitors, and mineralocorticoid receptor antagonists (MRAs) [18,19]. Among MRAs, eplerenone is a selective aldosterone blocker that has demonstrated beneficial effects on cardiac remodeling, fibrosis reduction, and clinical outcomes [7,16].

However, most existing studies focus primarily on the overall clinical benefits of eplerenone, while its effects on integrated neurohumoral regulation—particularly involving aldosterone, NT-proBNP, and the kallikrein–kinin system—remain insufficiently explored [13,14]. Moreover, data on its impact in the early stages of cardiorenal syndrome are limited.

Therefore, the aim of the present study was to evaluate the effects of eplerenone-based therapy on neurohumoral balance and renal function in patients with CRS associated with chronic heart failure.

Materials and methods

The study was conducted in 2024–2025 and included 115 patients diagnosed with cardiorenal syndrome (CRS) associated with chronic heart failure (CHF) (NYHA functional class II–III). All patients provided informed consent before participation.

The patients were divided into two groups:

- Group 1 (control group) – 57 patients who received standard therapy
- Group 2 (main group) – 58 patients who received standard therapy plus eplerenone

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Standard therapy included β-blockers (bisoprolol), angiotensin receptor–neprilysin inhibitor (sacubitril/valsartan), sodium-glucose cotransporter-2 inhibitor (empagliflozin), and diuretics. In the main group, eplerenone was prescribed at a dose of 25–50 mg per day. The duration of treatment was 12 weeks.

The following examinations were carried out in all patients before and after treatment:

- Neurohumoral markers: kallikrein, NT-proBNP, aldosterone
- Renal function: cystatin C and glomerular filtration rate (GFR), calculated using the CKD-EPI formula
- Clinical assessment: NYHA functional class, dyspnea, and exercise tolerance
- Instrumental methods: electrocardiography (ECG) and echocardiography

Blood samples were analyzed using enzyme-linked immunosorbent assay (ELISA) to determine serum levels of kallikrein, NT-proBNP, and aldosterone.

Statistical analysis was performed using Microsoft Excel software. The obtained data were expressed as mean values (M±m). Differences between groups were assessed using Student's t-test. Correlation analysis was performed using Pearson's correlation coefficient. A p-value <0.05 was considered statistically significant.

Results

Table 1. Changes in neurohumoral and renal parameters before and after treatment

Parameter	Control (baseline)	Control (12 weeks)	Eplerenone (baseline)	Eplerenone (12 weeks)
Kallikrein (ng/ml)	445±8	452±10	443±7.4	781±18.1*
NT-proBNP (pg/ml)	715±55	650±50	720±60	420±45*
Aldosterone (pg/ml)	275±18	260±20	280±20	190±15*
GFR (ml/min/1.73 m²)	54±1.3	55±1.4	54±1.2	62±1.5*

*p<0.05 compared to baseline

A total of 115 patients were included in the study. Among them, 57 patients were assigned to the control group, and 58 patients to the main group receiving eplerenone. At baseline, there were no significant differences between the groups in terms of age, gender distribution, NYHA functional class, and laboratory parameters (p>0.05), indicating comparability of the groups.

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Neurohumoral parameters

After 12 weeks of treatment, significant changes in neurohumoral markers were observed in the eplerenone group.

The level of kallikrein increased significantly from 443±7.4 ng/ml to 781±18.1 ng/ml ($p<0.001$), whereas no significant changes were observed in the control group ($p>0.05$).

NT-proBNP levels decreased markedly in the main group, from approximately 720±60 pg/ml to 420±45 pg/ml ($p<0.001$). In the control group, the decrease was less pronounced but still statistically significant ($p<0.05$).

Aldosterone levels also showed a significant reduction in the eplerenone group (from approximately 280±20 pg/ml to 190±15 pg/ml; $p<0.001$), while minimal changes were observed in the control group ($p>0.05$).

Renal function

Renal function assessment demonstrated a significant improvement in the eplerenone group.

Glomerular filtration rate (GFR), calculated based on cystatin C, increased from approximately 54±1.2 ml/min/1.73 m² to 62±1.5 ml/min/1.73 m² ($p<0.001$). In contrast, no statistically significant changes were observed in the control group ($p>0.05$)

Clinical parameters

Clinical evaluation showed improvement in NYHA functional class in patients receiving eplerenone.

A reduction in dyspnea and an increase in exercise tolerance were observed in the majority of patients in the main group. Although some improvement was also noted in the control group, it was less pronounced.

Correlation analysis

Correlation analysis revealed a moderate positive relationship between kallikrein levels and GFR ($r\approx0.55$; $p<0.001$).

A negative correlation was observed between kallikrein and NT-proBNP ($r\approx-0.48$; $p<0.001$), suggesting an association between increased kallikrein activity and reduced cardiac stress.

In addition, aldosterone levels showed a negative correlation with kallikrein ($r\approx-0.40$; $p<0.01$), reflecting the interaction between opposing neurohumoral systems.

Discussion

The results of the present study demonstrate that eplerenone-based therapy has a beneficial effect on neurohumoral balance and renal function in patients with cardiorenal syndrome associated with chronic heart failure.

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One of the key findings of this study is the significant reduction in aldosterone levels in patients receiving eplerenone. This result confirms the effectiveness of mineralocorticoid receptor blockade in suppressing excessive activation of the renin–angiotensin–aldosterone system (RAAS), which is known to play a central role in the progression of both cardiac and renal dysfunction [5,10,15].

In addition, a significant decrease in NT-proBNP levels was observed in the eplerenone group. This finding indicates a reduction in cardiac wall stress and improvement in hemodynamic status, which is consistent with previous studies demonstrating the clinical benefits of mineralocorticoid receptor antagonists in chronic heart failure [13,14].

An important aspect of this study is the evaluation of the kallikrein–kinin system. The observed increase in kallikrein levels in patients treated with eplerenone may suggest activation of protective neurohumoral pathways. The kallikrein–kinin system is known to exert vasodilatory, natriuretic, and anti-fibrotic effects, which may contribute to improved cardiovascular and renal outcomes [6,8].

At the same time, the increase in kallikrein levels may reflect an indirect effect of RAAS inhibition rather than a direct pharmacological action of eplerenone. This suggests a complex interaction between neurohumoral systems and highlights the need for further mechanistic studies.

Improvement in renal function, reflected by increased glomerular filtration rate based on cystatin C, supports the potential renoprotective effect of eplerenone. These findings are in agreement with previous studies indicating that RAAS blockade can positively influence renal hemodynamics and slow the progression of kidney dysfunction [8,9,17].

Correlation analysis further supports the interplay between neurohumoral systems. The positive relationship between kallikrein and GFR, along with the negative correlations between kallikrein and NT-proBNP and aldosterone, suggests that restoration of neurohumoral balance may be an important mechanism underlying clinical improvement in cardiorenal syndrome.

Modern treatment strategies for heart failure emphasize a combination of pharmacological agents, including ARNI, SGLT2 inhibitors, and mineralocorticoid receptor antagonists [4,18,20]. The results of the present study indicate that adding eplerenone to standard therapy provides additional benefits by targeting multiple pathophysiological pathways.

The clinical significance of this study lies in the potential use of eplerenone in the early stages of cardiorenal syndrome to improve both cardiac and renal function and to slow disease progression.

However, several limitations of the study should be acknowledged. The relatively short duration of follow-up (12 weeks) limits the assessment of long-term outcomes. In addition, the study was conducted in a single center with a relatively small sample size, which may affect the generalizability of the results. Further large-scale and long-term studies are required to confirm these findings.

Conclusion

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Eplerenone-based therapy has a positive effect on neurohumoral balance in patients with cardiorenal syndrome associated with chronic heart failure.

The results of the study demonstrated a significant decrease in aldosterone and NT-proBNP levels, along with an increase in kallikrein levels and improvement in renal function, as reflected by glomerular filtration rate.

These findings suggest that the therapeutic effect of eplerenone is associated not only with suppression of the renin–angiotensin–aldosterone system but also with activation of protective mechanisms of the kallikrein–kinin system.

Thus, the use of eplerenone as part of standard therapy in the early stages of cardiorenal syndrome may contribute to improved clinical outcomes and slowing of disease progression.

Further studies with larger sample sizes and longer follow-up periods are required to confirm these results.

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