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Original Research Article

Effect of lipoic acid combination with valsartan on diabetic nephropathy and associated adverse reactions

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Abstract

Purpose: *To investigate the effect of lipoic acid combination with valsartan on diabetic nephropathy (DN) and its associated adverse reactions.*
Methods: *A retrospective analysis was conducted on 120 patients who treated for DN at the Second Affiliated Hospital of Shenzhen University, China between August 2019 and October 2022. Based on different treatment approaches, control group comprised 55 patients receiving valsartan alone, while joint group consisted of 65 patients receiving a combination of valsartan and lipoic acid. Therapeutic effectiveness and adverse events were compared between the groups. Additionally, changes in blood glucose and renal function parameters were evaluated pre- and post-treatment.*
Results: *Post-treatment, both groups exhibited improvements in blood glucose and renal function parameters compared to pre-treatment values ($p < 0.05$). However, joint group demonstrated superior improvements in these parameters compared to control group ($p < 0.05$). Total efficacy was significantly higher in the joint group than in control group ($p < 0.05$). No significant differences were observed between the groups' incidence of adverse reactions ($p > 0.05$).*
Conclusion: *Concurrent therapy of lipoic acid and valsartan sly treats DN. It enhances the regulation of blood glucose levels and improves renal function with high safety. Further studies employing larger sample sizes and prospective designs with comprehensive patient follow-up are required to further validate and enhance the reliability of these findings.*

Keywords: *Lipoic acid, Valsartan, Diabetic nephropathy, Adverse reactions*

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INTRODUCTION

Diabetic nephropathy (DN) is a prevalent microvascular complication of diabetes, associated with significant chronic renal damage. Based on the extent of renal injury, DN is typically categorized into five stages [1]. Stage Ⅰ involves glomerular hyperfiltration and renal hypertrophy, while Stage Ⅱ is marked by intermittent proteinuria. These initial stages often lack overt symptoms and histopathological evidence, posing challenges in early detection [2]. Progression to Stage Ⅲ signifies early DN, characterized by microalbuminuria, necessitating drug intervention and management adjustments. In Stage IV, patients enter the clinical phase of DN, with a gradual decline in glomerular filtration rate, heightening the uremia risk. Stage Ⅴ

represents end-stage renal failure, where severe renal dysfunction may require dialysis or kidney transplantation [3]. Globally, over 400 million individuals have diabetes, and approximately 30%-40% of them are at risk of developing DN. The morbidity and mortality rates of DN have been steadily rising [4], highlighting the urgency of effective prevention and control measures in global public health.

The treatment strategy for DN primarily involves managing blood glucose and lipid levels, controlling hypertension, and preventing or treating associated complications [5]. Lipoic acid, commonly known as vitamin B1, is a vital water-soluble vitamin that supports the proper functioning of the body and nervous system. Furthermore, studies has indicated its potential in mitigating the progression of DN [6].

Numerous studies have demonstrated the therapeutic benefits of lipoic acid in DN. For instance, a clinical trial involving diabetic patients exhibited the effectiveness of lipoic acid in significantly slowing down the decline in glomerular filtration rate and reducing the occurrence of proteinuria [7]. Valsartan, an angiotensin II receptor antagonist, serves as an antihypertensive agent. Its primary mechanism lies in blocking angiotensin receptors, leading to vasodilation and a subsequent reduction in blood pressure [8]. Valsartan finds applications in the treatment of hypertension, congestive heart failure, as well as DN, offering long-lasting and stable effects with minimal adverse effects. Studies have shown that valsartan effectively reduces 24-hour urinary protein excretion in patients with hypertension and diabetes, while also mitigating the rate of kidney function decline [9]. Therefore, a comprehensive approach tailored to the individual patient's condition is crucial in managing DN. Implementing effective intervention measures is essential to control disease progression, preserve renal function, and enhance the patient's overall quality of life.

The objective of this study is to assess the clinical efficacy and safety profile of a combined therapy utilizing lipoic acid and valsartan in the treatment of diabetic nephropathy (DN). The study aims to contribute valuable insights and reliable references to support clinical diagnosis and management strategies for this condition.

METHODS

Patient profile

A retrospective evaluation was conducted on the 120 individuals who received treatment at the Second Affiliated Hospital of Shenzhen University, Shenzhen, China between August 2019 and October 2022. Based on different treatment approaches, control group comprised 55 DN patients who received valsartan alone, while joint group consisted of 65 patients who received a combined administration of valsartan and lipoic acid. The study protocol received approval from the Medical Ethics Committee of the Second Affiliated Hospital of Shenzhen University (approval no. KY0031541), and adhered to the guidelines of the Declaration of Helsinki [10].

Inclusion criteria

Patients fulfilling diagnostic criteria for DN [11]; patients with stage 3-4 urinary protein and 3-4 estimated glomerular filtration rate; patients with no prior medication treatments; patients with normal mental state; patients with normal function of vital organs (heart, liver); patients with complete clinical data.

Exclusion criteria

Patients with drug allergy and contraindications treated in this study; patients with kidney disease caused by primary or other factors; patients with severe hypertension; patients with low compatibility and compliance; patients with concurrent endocrine diseases; patients with coagulation dysfunction; patients with infectious or immune diseases; pregnancy and lactation.

Therapeutic regimens

Patients received standard routine treatment. This included dietary control and exercise to manage diabetes. Patients were prescribed daily doses of 5 mg linagliptin and 10 mg dapagliflozin for glycemic control. Additionally, antihypertensive therapy with 30 mg nifedipine controlled-release tablets once daily aimed to maintain blood pressure below 140/90 mmHg. Lipid regulation and microcirculation promotion were also integral parts of the comprehensive treatment plan.

In the control group, patients received 80 mg valsartan (Beijing Novartis Pharmaceutical Co. Ltd, SFDA approval no. H20040217) orally once daily for 14 days.

Joint group followed the protocol for control group but also received combination therapy with lipoic acid. This involved an intravenous infusion of 0.6 g lipoic acid (Yabao Pharmaceutical Group Co. Ltd, SFDA approval no. H20203417) in 250 mL of 0.9 % sodium chloride solution,

administered daily for 14 days under shade conditions. In the morning, fasting venous blood samples (5 mL) were collected from both groups. The specimens were centrifuged at 3500 rpm for 5 min, and the supernatant was stored at low temperatures for further analysis.

Evaluation of parameters/indices

Renal function

Twenty four-hour urine was collected. Renal function was assessed by determining urinary albumin excretion rates (UAER), Beta-2 microglobulin (β2-MG), cystatin C (Cys-C), and serum creatinine (SCr).

Blood sugar indices

Fasting venous blood (5 mL) was collected from individuals in both groups in the morning. Postprandial blood samples (3 mL) were obtained from the median elbow vein after 2 h to measure 2 h postprandial glucose (2hPG). Other blood sugar indices, including fasting blood glucose (FBG) and flavin mononucleotide (FMN), were assessed using an automated biochemical diagnostic instrument before and after treatment.

Therapeutic effectiveness/efficacy

Therapeutic effectiveness was compared between control and joint groups. The total effective rate (TE) was calculated by summing the numbers of markedly effective (ME) and effective (E) cases, dividing by the total patient (N) count, and multiplying by 100 %. Criteria for efficacy evaluation are detailed in Table 1.

Adverse effect

Adverse effects were compared between the two groups.

Statistical analysis

The collected data were analyzed using SPSS 20.0 software (SPSS Inc, Chicago, IL, USA), and graphical presentations were created with GraphPad Prism 8. Chi-square test was applied to compare categorical variables, while paired t-tests were used for intra-group comparisons and independent sample t-tests for inter-group comparisons. Statistical significance was set at $p < 0.05$, indicating a significant difference.

RESULTS

Baseline characteristics

The two groups were comparable in terms of gender, body mass index, age, disease duration, and educational level ($p > 0.05$; Table 2).

Blood sugar parameters

A comparison of blood sugar indices revealed no significant differences in FBG, 2hPG, and FMN between control and joint groups before treatment ($p > 0.05$). However, following treatment, joint group exhibited significant reductions in these indices compared to control group ($p < 0.05$). Within-group comparisons also showed significant decreases in FBG, 2hPG, and FMN post-treatment compared to pre-treatment levels in both groups ($p < 0.05$; Figure 1).

Renal function

A comparison of renal function indices, including UAER, β2-MG, Cys-C, and SCr, revealed no significant differences between control group and joint group before treatment ($p > 0.05$). Nevertheless, after treatment, joint group exhibited significant improvements in these indices compared to control group ($p < 0.05$). Similarly, within-group comparisons demonstrated significant reductions in UAER, β2-MG, Cys-C, and SCr post-treatment compared to pre-treatment levels in both groups ($P < 0.05$) (Figure 2).

Therapeutic effect

A comparative analysis of the therapeutic effects revealed a significantly higher total effective rate in joint group compared to control group ($p = 0.005$; Table 3).

Table 1: Criteria for assessing clinical efficacy

Efficacy rating	Evaluative criteria
Markedly effective	The patients experienced complete resolution of clinical symptoms, restoration of normal renal function, and a reduction in urinary albumin excretion rate (UAER) by more than 50%.
Effective	Clinical symptoms were relieved, renal function was improved, and UAER decreased by 30% ~ 50%.
Ineffective	Clinical symptoms and renal function had not improved or deteriorated.

Table 2: Comparison of basic information

Factor	Variable	Control group (n = 55)	Joint group (n = 65)	χ^2	P-value
Age					
	≤ 45 years old	18	24	0.231	0.631
	> 45 years old	37	41		
Gender					
	Male	29	28	1.113	0.292
	Female	26	37		
Body mass index					
	≤ 21 kg/m^2	33	36	0.259	0.610
	> 21 kg/m^2	22	29		
Course of disease (year)				1.494	0.222
	≤ 5	21	18		
	> 5	34	47		
Educational level					
	Below junior college	29	40	0.946	0.331
	Junior college and above	26	25		

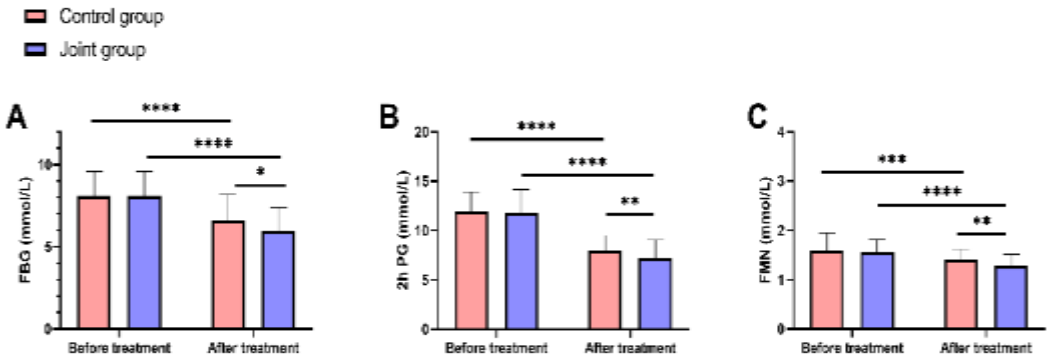

Figure 1: Comparison of blood sugar-related parameters. (A) Changes in fasting blood glucose (FBG) level; (B) Changes in 2h postprandial glucose (PG) level; (C) Changes in flavin mononucleotide (FMN) level. ***Note:*** *P < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.0001

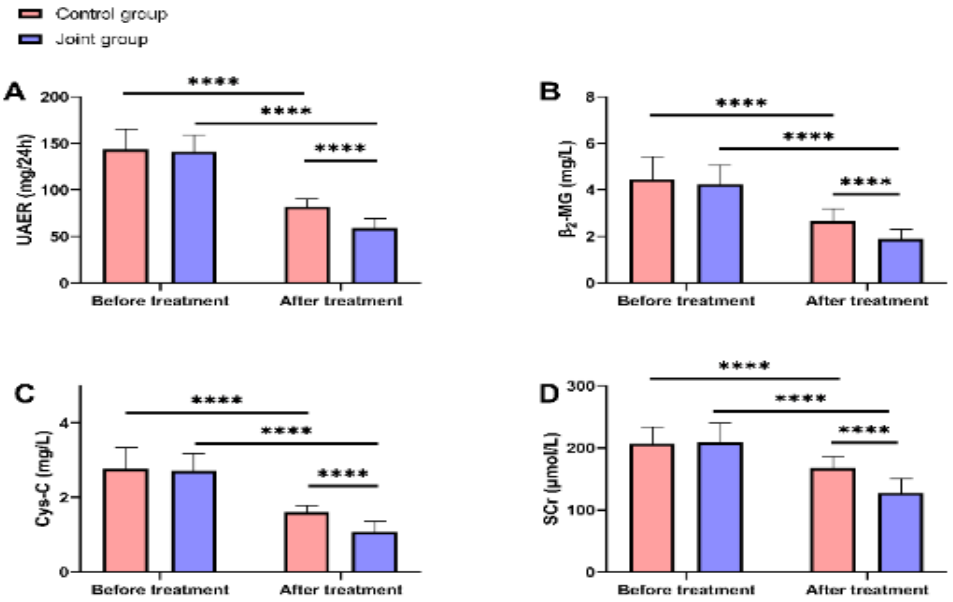

Figure 2: Comparison of renal function parameters. (A) Changes in urinary albumin excretion rates (UAER) level; (B) Changes in Beta-2 microglobulin (β2-MG) level; (C) Changes in Cystatin C (Cys-C) level; (D: Changes in serum creatinine (SCr) level. ***Note:*** ****p < 0.0001

Table 3: Comparison of therapeutic effect/efficacy

Group	Markedly effective	Effective	Ineffective	Total effective rate
Control group (n=55)	10 (18.18)	29 (52.73)	16 (29.09)	39 (70.91)
Joint group (n=65)	31 (47.69)	28 (43.08)	6 (9.23)	59 (90.77)
χ^2				7.848
P-value				0.005

Table 4: Incidence of adverse events

Group	Dyspnea	Nausea	Fatigue	Feeling of fullness in the head	Total adverse reactions
Control group (n=55)	2 (3.64)	0	0	2 (3.64)	4 (7.27)
Joint group (n=65)	0	1 (1.54)	4 (6.15)	0	5 (7.69)
χ^2					0.008
P-value					0.931

Incidence of adverse reactions

The analysis of adverse reactions showed that control group had an incidence of 7.27 %, while joint group had an incidence of 7.69 %. No statistically significant difference was observed between the two groups ($p > 0.05$; Table 4).

DISCUSSION

The incidence of DN has been steadily rising in recent years, largely attributed to shifts in lifestyle patterns [12]. Unhealthy behaviors, including consumption of high-fat and high-sugar diets, inadequate physical activity, and smoking, have been implicated as key risk factors for diabetes development. Among diabetics, inappropriate dietary choices, excessive alcohol intake, overeating, and obesity exacerbate renal dysfunction, ultimately leading to or worsening DN.

Diabetic nephropathy pathogenesis is intricate, with chronic hyperglycemia serving as the primary culprit [13]. This hyperglycemic state damages glomerular micro vessels, disrupting kidney function, which may gradually decline over time. Additional factors such as hypertension, oxidative stress, genetics, and metabolic disorders also contribute to the pathogenesis of DN [14]. Approximately 30 to 40 % of both type 1 and type 2 diabetes patients may suffer from kidney damage, with 5 % of diagnosed type 2 diabetes patients already exhibiting signs of DN [15].

Diabetic nephropathy lead to various complications, including renal dysfunction, hypertension, water and electrolyte imbalances, and abnormal bone metabolism, significantly contributing to mortality among diabetic patients [16]. Regular monitoring of urine and blood tests is crucial for diabetic individuals to detect early signs of DN, enabling prompt intervention and appropriate treatment to mitigate disease progression.

The objective of DN treatment is to safeguard kidney function, manage the disease, alleviate symptoms, and prevent complications. Standard DN treatment strategies include glycemic control, blood pressure management, dietary protein restriction, pharmacological intervention, and other targeted approaches. Selecting an appropriate therapy tailored to the individual's needs and ensuring its administration under the supervision of a healthcare professional is crucial to optimize therapeutic outcomes.

Lipoic acid, renowned for its antioxidant properties, is commonly used to treat diabetic polyneuropathy [17]. It safeguards and mitigates the impact of hyperglycemia on the glomerulus, thereby reducing the risk of DN. Additionally, numerous clinical trials have established valsartan's effectiveness in DN treatment, demonstrating its ability to decrease the risk of cardiac events, including myocardial infarction, and decelerate renal function decline [18]. However, monotherapy may not achieve the optimal therapeutic effect in DN. Hence, this study aimed to investigate the efficacy of combining these two drugs. Findings revealed a significantly higher total effective rate in the combined therapy group compared to control group, indicating that this combination leverages the strengths of both drugs, complementing each other to significantly enhance therapeutic outcomes for patients. Furthermore, comparative analysis of blood sugar-related indices before and after treatment indicate that post-treatment FBG, 2h PG, and FMN levels were significantly reduced in both groups compared to pre-treatment levels. Notably, joint group exhibited more substantial decreases in these indices compared to control group, indicating that the combination of valsartan and lipoic acid significantly improved blood sugar control and

treatment outcomes. Valsartan monotherapy may have limitations in treating DN, whereas the synergistic combination of valsartan and lipoic acid enhances glycemic control and symptom relief. Jeffrey *et al* [19] reported that lipoic acid reduce the risk of diabetes and its complications through various mechanisms, including antioxidant and anti-inflammatory effects, as well as improved insulin sensitivity, aligning with the findings in this study.

Kidney health evaluation before and after treatment showed reduced levels of UAER, β2-MG, Cys-C, and SCr post-treatment compared to pre-treatment in both groups. However, joint group showed more significant improvements in these kidney function markers compared to control group, indicating the superiority of combined therapy in improving kidney function and treatment outcomes. The combined administration of lipoic acid and valsartan not only mitigates kidney damage caused by abnormal blood sugar and blood pressure levels but also decreases glomerular filtration pressure, thereby slowing the progression of renal injury. Previous study [20] demonstrated that the concurrent use of these agents effectively reduces urinary albumin levels and oxidative stress in DN patients, improving renal function and offering a promising pharmacological approach for managing this disease which is consistent with these findings.

No significant differences occurred between control group and joint group with regards to their adverse effects. This indicates that the combination of lipoic acid and valsartan significantly improves renal injury in DN patients, enhancing therapeutic efficacy, while maintaining a high level of safety without increasing adverse reactions.

Limitations of this study

This study is retrospective and used relatively small sample size, which may have limited the uniformity and reliability of the findings compared to randomized controlled trials. Additionally, the lack of patient follow-up precluded the assessment of long-term treatment effects and prognosis.

CONCLUSION

The combined use of lipoic acid and valsartan is effective in the management of DN, regulates blood sugar levels, improves renal function, and exhibits a high level of safety. Further studies employing larger sample sizes and prospective designs with comprehensive patient follow-up are needed to validate and enhance the reliability of these findings.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Minqin Wang and Jiaying Luo conceived and designed the study, and drafted the manuscript. Minqin Wang and Jisu Xue collected, analyzed and interpreted the experimental data. All authors revised the manuscript for important intellectual content. All authors read and approved the final draft of the manuscript for publication.

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