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Original Article

Efficacy of bumetanide tablets combined with valsartan in the treatment of elderly patients with chronic glomerulonephritis and its effects on renal function and hemodynamics

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Abstract: Objective: This study was designed to determine the efficacy of bumetanide tablets combined with valsartan for the treatment of elderly patients with chronic glomerulonephritis (CGN) and its effects on renal function and hemodynamics. Methods: Data from 122 elderly patients with CGN admitted to Pingdingshan First People's Hospital from April 2019 to January 2020 were analyzed retrospectively. Among them, 65 patients treated with bumetanide tablets combined with valsartan were assigned to a study group and the other 57 patients treated with bumetanide tablets alone were assigned to a control group. The clinical efficacy, renal function, hemodynamics and inflammatory factors of the two groups were compared, and the incidence of adverse reactions during treatment was calculated. The risk factors of unfavorable prognosis were analyzed by multiple logistics regression. Results: The study group showed a significantly higher total response rate than the control group ($P<0.05$), and no notable difference was found in the incidence of adverse reactions between the two groups ($P>0.05$). Before treatment, the examination results of renal function and hemodynamics of the two groups were not significantly different ($P>0.05$), and the results of both groups were improved after treatment ($P<0.05$). Furthermore, the study group showed significantly higher levels of renal function and hemodynamics and lower levels of inflammatory factors than the control group after treatment ($P<0.05$). Older age (OR: 1.883, 95% CI: 1.226-2.892), higher post-treatment blood urea nitrogen (OR: 4.328, 95% CI: 1.117-16.778) and lower post-treatment end-diastolic flow velocity (OR: 0.419, 95% CI: 0.117-0.992) were independent risk factors for unfavorable prognosis of patients. Conclusion: Bumetanide tablets combined with valsartan are remarkably effective for elderly patients with CGN. This combined method can substantially improve the renal function and hemodynamics of the patients, so it has a high clinical application value in the future.

Keywords: Bumetanide tablets, combined valsartan, chronic glomerulonephritis, renal function, hemodynamics, inflammatory factor

Introduction

With the aging of society, an increasing number of elderly patients are suffering from chronic diseases, among which chronic kidney disease requires attention. It maintains a high incidence (8-16%) globally, with no obvious clinical symptoms at the initial stage [1-3]. Chronic glomerulonephritis (CGN) is a primary form of chronic kidney disease and the primary cause of end-stage kidney disease [4, 5]. The occurrence of CGN is related to autoimmune regulation. Abnormal neutrophils and lymphocytes release cytokines to mediate inflammation, triggering glomerular injury in patients [6]. Patients with CGN may suffer clinical symptoms such as proteinuria and hematuria at the initial stage, and have decline renal function in the meantime, and CGN can gradually develop into renal failure as it progresses [7, 8]. Reportedly, the renal microcirculation and blood vessel status of CGN patients will change, thus impacting their hemodynamics. Therefore, understanding the hemodynamics of patients is often helpful to understand the disease progression of patients [9, 10].

The Valsartan tablet is an Ang II receptor blocker, which can inhibit Ang II by binding to the Ang II receptor, thus promoting the proliferation of glomerular Mesangial cells, reducing intraglomerular hypertension, and gradually reducing the urinary protein filtration rate and the content of proteinuria [11]. However, according to prior research, valsartan has a slow effect, and its recovery effect is not favorable for patients' renal function, so it is often necessary to combine it with other therapeutic drugs in clinical application [12]. Bumetanide is a diuretic, which can inhibit the activity of sodium-potassium-chloride cotransporters (NKCC) to dilate blood vessels and contribute to lowering blood pressure and preventing renal blood perfusion insufficiency [13]. It has been reported that bumetanide can reduce sodium reabsorption in the glomerulus and induce diuresis after inhibiting NKCC [14]. Currently, the efficacy of a single drug is not significant, and treatment with bumetanide tablets and valsartan for CGN is rarely reported. Accordingly, this study used bumetanide tablets combined with valsartan to treat elderly patients with CGN, and then analyzed the clinical response of the combination in the patients, and observed the changes of their renal function and hemodynamics.

Methods and data

Patient information

A total of 122 elderly patients with CGN admitted to Pingdingshan First People's Hospital from April 2019 to January 2020 were studied retrospectively. Among them, 65 patients treated with bumetanide tablets combined with valsartan were assigned to a study group, including 42 males and 23 females, with a mean age of (75.60±7.13) years and a course of disease of (4.37±1.53) years. The other 57 patients treated with bumetanide tablets alone were assigned to a control group, with 33 males and 24 females, a mean age of (74.97±6.6) years and a course of disease of (4.12±1.67) years. This study was performed after being approved of by the Ethics Committee of Pingdingshan First People's Hospital (IRB-20190112), with informed consent forms signed by all patients.

Inclusion and exclusion criteria

The inclusive criteria: Patients diagnosed with CGN [15], patients with proteinuria that worsened within 2 months, patients with edema and foamy urine that appeared in different degrees, patients with 1-3 g/d urine protein, patients with glomerular filtration rate >30 mL/min/1.73 m^2, patients who had never received any dialysis treatment, and patients with the required clinical data.

The exclusion criteria: Patients with other liver or kidney diseases, patients with stage 4-5 chronic kidney disease, patients with severe cardiovascular or cerebrovascular diseases, patients with severe inflammation or infection, patients with severe immunodeficiency, patients who were allergic to the treatment drugs, patients with unfavorable compliance, patients who were pregnant or lactating.

Treatments

After admission, both groups were given basic treatment of acid-base balancing, water-electrolyte balancing, blood pressure reducing and lipid regulating. On this basis, the control group was given valsartan tablets (Beijing Novartis Pharma Ltd.; Number: 161109) orally, 80 mg once a day. On the basis of the control group, the study group was additionally treated with bumetanide tablets (Guilin Nantang Pharmaceutical Co., Ltd.; Number: 161028) orally, 0.5 mg once, twice a day. Both groups were treated for 12 weeks.

Outcome measures

(1) The efficacy on the two groups after treatment was compared. Markedly effective: The clinical symptoms of the patient disappeared or were greatly relieved, with urine protein quantitative (24 h) decrease by ≥50%, and the renal function was basically normal. Effective: The clinical symptoms of the patient were relieved, and the urine protein quantity (24 h) was reduced but less than 50%. Ineffective: None of above criteria was met, or the disease was aggravated. Total response rate = (the number of cases (markedly effective + effective)/total number of cases) ×100%.

(2) The adverse reactions of the two groups were counted during treatment.

(3) The renal function of patients before and after treatment was evaluated, including the levels of serum creatinine (SCr), blood urea

nitrogen (BUN) and urinary albumin excretion rate (UAER). Before and after treatment, 5 mL fasting elbow venous blood was sampled from each patient in the two groups, followed by 15-min centrifugation (3500 r/min). The separated serum was stored at -80°C for later analysis. An Olympus AU5400 automatic biochemical analyzer was adopted to determine SCr and BUN in the serum, and a Beckman MMAGE 800 automatic urinary protein analyzer was adopted to analyze UAER.

(4) Hemodynamic indicators of the two groups were evaluated. Peak systolic flow velocity (PSFV), end-diastolic flow velocity (EDFV) and resistance index (RI) of the renal artery were measured by Mindray DC-7 color Doppler ultrasound before and after treatment.

(5) Serum IL-6 and TNF-α levels were determined through ELISA before and after treatment with corresponding ELISA kits from American R&D Systems (D6050, DTA00D).

(6) All patients were followed up for 1 year through outpatient reexamination once every 3 months. The prognosis of the patients was analyzed, and the risk factors of unfavorable prognosis were analyzed by multivariate analysis. Development to end-stage renal disease (ESRD) indicates an unfavorable prognosis.

Statistical analyses

This study used SPSS 20.0 (Chicago SPSS Co., Ltd., USA) for statistical analysis of the collected data, and used Graphpad Prism 7 (San Diego GraphPad Software Co., Ltd., USA) for visualization of the data. The counting data (%) were analyzed via Chi-square test, and presented via X^2. All measurement data (Mean ± SD) were in normal distribution. Their inter-group comparison was conducted using independent-sample t test, and their intra-group comparison was performed using paired t test, and presented by t. Multivariate logistics regression analysis was used to detect the risk factors affecting prognosis. P<0.05 denotes a significant difference.

Results

Baseline data

In terms of baseline data, no significant difference was found between the two groups in age, course of disease, sex, body mass index, diabetes history, smoking history, alcoholism history, place of residence and pathological type (P>0.05, **Table 1**).

Comparison of efficacy

The study group yielded a significantly higher total response rate than the control group (93.85% vs. 80.70%, P<0.05, **Table 2**).

Incidence of adverse reactions in the two groups

Nausea, rash, diarrhea and dizziness were the adverse reactions in the study group, and nausea, rash and diarrhea were found in the control group. The incidence of adverse reactions of the two groups was not greatly different (P>0.05, **Table 3**).

Effects of treatments on patients' renal function

No notable difference was found in SCr, BUN and UAER between the two groups before treatment (P>0.05). While after treatment, the SCr, BUN and UAER of both groups decreased significantly (P<0.05), with significantly lower levels in the study group than those in the control group (P<0.05, **Figure 1**).

Effect on patients' hemodynamic indexes

Before treatment, renal hemodynamic indexes, PSFV, EDFV, RI were not greatly different in the two groups (P>0.05). After treatment, PSFV and EDFV increased significantly, while RI decreased significantly in both groups. The post-treatment increases and decrease were more significant in the study group than those in the control group (P<0.05, **Figure 2**).

Effects on inflammation in patients

Before treatment, serum IL-6 and TNF-α levels were not greatly different in the two groups (P>0.05), while after treatment, IL-6 and TNF-α in both groups decreased significantly (P<0.05), with significantly lower levels in the study group than those in the control group (P<0.05, **Figure 3**).

Prognosis of patients and univariate analysis

One year later, 6 patients in the study group developed to ESRD and 7 in the control group

Table 1. Baseline data

	Study group (n=65)	Control group (n=57)	X^2/t	*P*-value
Age (years)	75.60±7.13	74.97±6.6	0.504	0.615
Course of disease (years)	4.37±1.53	4.12±1.67	0.863	0.390
Sex			0.579	0.447
Male	42 (64.62)	33 (57.89)		
Female	23 (35.38)	24 (42.11)		
BMI (kg/m^2)	22.58±1.69	22.24±1.63	1.127	0.262
Diabetes mellitus			0.629	0.428
Yes	10 (15.38)	6 (10.53)		
No	55 (84.62)	51 (89.47)		
Smoking history			0.364	0.546
Yes	13 (20.00)	9 (15.79)		
No	52 (80.00)	48 (84.21)		
Alcohol history			0.057	0.811
Yes	6 (9.23)	6 (10.53)		
No	59 (90.77)	51 (89.47%)		
Place of residence			0.382	0.536
Urban area	47 (72.31)	44 (77.19)		
Rural area	18 (27.69)	13 (22.81)		
Pathological type			1.225	0.747
Membranoproliferative glomerulonephritis	26 (40.00)	25 (43.86)		
Membranous capillary glomerulonephritis	18 (27.69)	18 (31.58)		
Membranous nephropathy	13 (20.00)	10 (17.54)		
Focal segmental glomerulosclerosis	8 (12.31)	4 (7.02)		

BMI: body mass index.

Table 2. Therapeutic efficacy

	Study group (n=65)	Control group (n=57)	X^2	*P*-value
Markedly effective	29 (44.62)	20 (35.09)	1.147	0.284
Effective	32 (49.23)	26 (45.61)	0.159	0.690
Ineffective	4 (6.15)	11 (19.30)	4.866	0.027
Total response rate	61 (93.85)	46 (80.70)	4.866	0.027

Table 3. Adverse reaction

	Study group (n=65)	Control group (n=57)	X^2	*P*-value
Nausea	2 (3.08)	1 (1.75)		
Rash	3 (4.62)	2 (3.51)		
Diarrhea	2 (3.08)	2 (3.51)		
Dizzy	1 (1.54)	0 (0.00)		
Total adverse reactions	8 (12.31)	5 (8.77)	0.399	0.528

developed ESRD, so the prognosis was not greatly different in the two groups. According to the prognosis, the patients were grouped into an unfavorable prognosis group and a favorable prognosis group. Then the baseline data of these two groups were compared, and significant differences were found between them in age, course of disease, history of alcoholism, post-treatment SCr, post-treatment BUN, post-treatment UAER, post-treatment PSFV, post-treatment EDFV, post-treatment IL-6 and post-treatment TNF-α (**Table 4**).

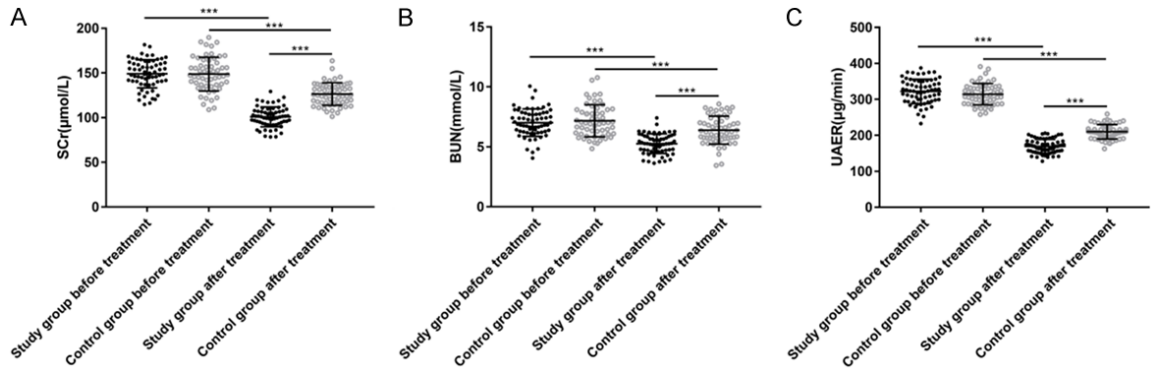

Figure 1. Changes of renal function before and after treatment. A. After treatment, the SCr in both groups decreased significantly (P<0.001), with a significantly lower level in the study group than that in the control group (P<0.001). B. After treatment, the BUN in both groups decreased significantly (P<0.001), with a significantly lower level in the study group than that in the control group (P<0.001). C. After treatment, the UAER in both groups decreased significantly (P<0.001), with a significantly lower level in the study group than that in the control group (P<0.001). Note: ***P<0.001. SCr: serum creatinine, BUN: blood urea nitrogen, UAER: urinary albumin excretion rate.

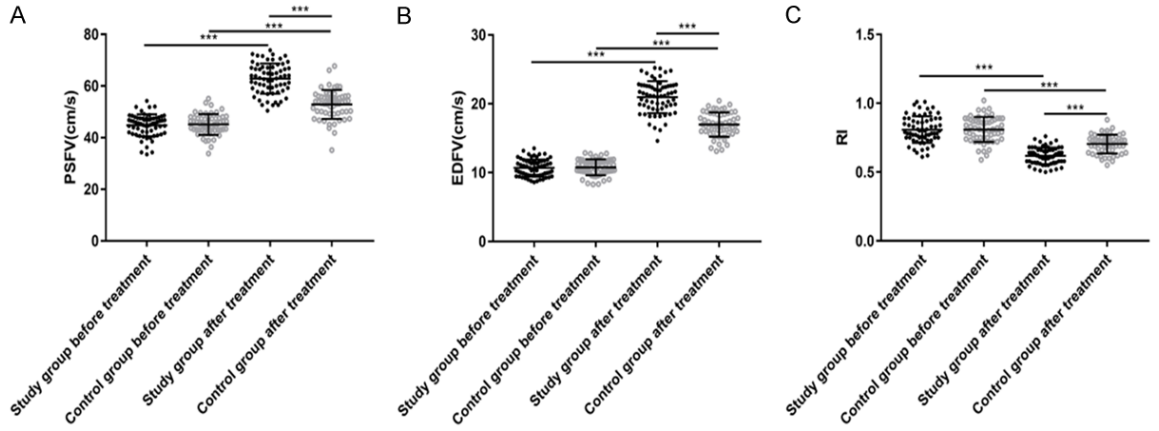

Figure 2. Changes of hemodynamics in patients before and after treatment. A. After treatment, the PSFV in both groups increased significantly (P<0.001), with a significantly higher level in the study group than that in the control group (P<0.001). B. After treatment, the EDFV in both groups increased significantly (P<0.001), with a significantly higher level in the study group than that in the control group (P<0.001). C. After treatment, the RI in both groups decreased significantly (P<0.001), with a significantly lower level in the study group than that in the control group (P<0.001). Note: ***P<0.001. PSFV: peak systolic flow velocity, EDFV: end-diastolic flow velocity, RI: resistance index.

Multivariate analysis of prognosis

Multiple logistics regression analysis showed that older age (OR: 1.883, 95% CI: 1.226-2.892), higher post-treatment BUN (OR: 4.328, 95% CI: 1.117-16.778) and lower post-treatment EDFV (OR: 0.419, 95% CI: 0.117-0.992) were independent risk factors for unfavorable prognosis (**Table 5**).

Discussion

The pathogenesis of CGN is complex, and it is primarily considered to be an immune-mediated inflammatory reaction [16]. The glomerular filtration barrier is affected by immune complexes. Destruction of capillary permeability and the reabsorption of protein by the renal tubule cause the protein to enter the urine to form proteinuria [17]. Additionally, there are obvious changes in renal structure in elderly patients, including serious glomerulosclerosis, renal tubule atrophy and renal interstitial fibrosis, which increase the distance between renal tubules and increases the interstitial volume, as well as increases the difficulty of treatment [18, 19].

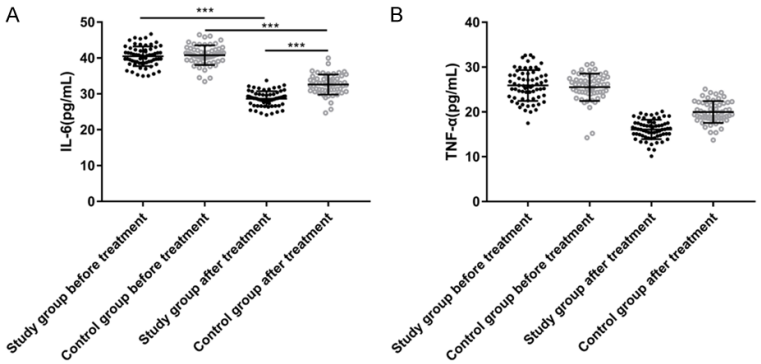

Figure 3. Changes of inflammation level before and after treatment. A. After treatment, IL-6 in both groups decreased significantly (P<0.001), with a significantly lower level in the study group than that in the control group (P<0.001). B. After treatment, TNF-α in both groups decreased significantly (P<0.001), with a significantly lower level in the study group than that in the control group (P<0.001). Note: ***P<0.001.

Comparison of efficacy in the two groups showed that the study group yielded a significantly higher total response rate than the control group (93.85% vs. 80.70%). Then, the changes of patients' renal function before and after treatment were compared. According to the results, both the combined treatment and valsartan alone improved the renal function of patients, but after treatment, the study group showed remarkably lower levels of SCr, BUN and UAER than the control group, indicating that the combined treatment had a better effect on improving the renal function of CGN patients. Valsartan can dilate glomerular arterioles, improve glomerular blood pressure and the selective permeability of filtration membranes, alleviate high filtration rates and reduce urinary protein in patients with CGN, thus improving renal function [20]. Bumetanide is a powerful diuretic and acts by suppressing NKCC, which can dilate blood vessels, reduce blood pressure and prevent renal blood perfusion deficiency [21]. Additionally, it can inhibit the activity of prostaglandin decomposing enzyme and increase the content of prostaglandin E2, which can dilate blood vessels, reduce renal vascular resistance and increase renal vascular blood flow, especially the deep blood flow of the renal cortex [22]. A key feature of the glomeruli is the infiltration of inflammatory cells, especially the massive accumulation of T cells, monocytes and macrophages, which release inflammatory factors and influence the progression of nephritis [23]. Excessive platelet aggregation may increase the risk of renal vein thrombosis and deepen renal pathological damage. In this study, the decrease of IL-6 and TNF-α in patients after combined treatment was more notable, indicating that the combination of the two drugs can deliver better therapeutic effect in inhibiting the inflammatory reaction.

SCr and BUN levels can both reflect patients' glomerular filtration capacity, and UAER can reflect patients' disease progression [24]. The present study showed that the combined therapy was more effectively in improving the renal function of patients. Bumetanide can inhibit the reabsorption of sodium ions in renal tubules and proximal tubules, effectively maintain electrolyte balance, improve renal microcirculation, reduce extracellular fluid osmotic pressure, improve renal hyperperfusion, high filtration and high transmembrane pressure, delay or inhibit glomerulosclerosis, and protect patients' surviving renal function [25]. Bumetanide tablets can dilate renal vessels, substantially reduce renal vascular resistance, increase deep blood flow in renal cortex, and improve glomerular filtration rate and renal function [26], which was also found in the detection of hemodynamic indexes of patients in the present study. Patients treated with the combination of drugs showed better PSFV, EDFV and RI than those treated with valsartan alone after treatment. Damaged glomeruli can increase filtration pressure, and when the kidney is in a state of high osmotic pressure it will affect the blood circulation of the renal aorta and segmental artery, resulting in renal microvasospasm and renal tissue ischemia [27]. PSFV, EDFV and RI can help evaluate the renal blood flow. The increase in PSFV and EDFV and the decrease in RI indicate notable improvement of the renal blood supply. The deficiency of renal effective blood flow is usually due to the high osmotic pressure of the kidney, resulting in hematuria and proteinuria, seriously affecting renal function [28]. The combination of valsartan and bumetanide can act on the lesion through different mechanisms, reduce renal vascular resistance, promote blood supply and

Table 4. Multivariate analysis

	Unfavorable prognosis group (n=13)	Favorable prognosis group (n=109)	X^2/t	*P* value
Age (years)	82.85±4.06	74.40±6.59	4.512	<0.001
Course of disease (years)	5.15±1.63	4.15±1.56	2.175	0.032
Sex			0.370	0.543
Male	9 (69.23)	66 (60.55)		
Female	4 (30.77)	43 (39.45)		
BMI (kg/m^2)	22.47±1.98	22.41±1.63	0.123	0.903
Diabetes mellitus			1.267	0.260
Yes	3 (23.08)	13 (11.93)		
No	10 (76.92)	96 (88.07)		
History of smoking			1.597	0.206
Yes	4 (30.77)	18 (16.51)		
No	9 (69.23)	91 (83.49)		
History of alcohol			2.876	0.090
Yes	3 (23.08)	9 (8.26)		
No	10 (76.92)	100 (91.74)		
Place of residence			0.772	0.380
Urban area	11 (84.62)	80 (73.39)		
Rural area	2 (15.38)	29 (26.61)		
Pathological type			0.818	0.845
Membranoproliferative glomerulonephritis	6 (46.15)	45 (41.28)		
Membranous capillary glomerulonephritis	3 (23.08)	33 (30.28)		
Membranous nephropathy	2 (15.38)	21 (19.27)		
Focal segmental glomerulosclerosis	2 (15.38)	10 (9.17)		
Post-treatment SCr (μmol/l)	127.29±15.34	111.04±16.88	3.310	0.001
Post-treatment BUN (mmol/L)	7.02±0.99	5.64±1.07	4.427	<0.001
Post-treatment UAER (μg/min)	204.28±22.54	186.56±28.63	2.151	0.034
Post-treatment PSFV (cm/s)	50.82±7.17	59.03±7.19	3.893	<0.001
Post-treatment EDFV (cm/s)	15.96±1.77	19.47±2.76	4.468	<0.001
Post-treatment RI	0.69±0.07	0.65±0.08	1.724	0.087
Post-treatment IL-6 (pg/mL)	32.48±3.07	30.25±3.09	2.461	0.015
Post-treatment TNF-α (pg/mL)	20.55±2.54	17.63±2.95	3.418	<0.001
Therapeutic regimen			0.297	0.586
Single treatment	7 (53.85)	50 (45.87)		
Combined treatment	6 (46.15)	59 (54.13)		

BMI: body mass index, SCr: serum creatinine, BUN: blood urea nitrogen, UAER: urinary albumin excretion rate, PSFV: peak systolic flow velocity, EDFV: end-diastolic flow velocity, RI: resistance index.

Table 5. Multivariate analysis

	B	S.E,	Wals	Sig.	Exp (B)	95% C.I of EXP (B)	
						Lower limit	Upper limit
Age	0.633	0.219	8.363	0.004	1.883	1.226	2.892
Post-treatment BUN	1.465	0.691	4.492	0.034	4.328	1.117	16.778
Post-treatment EDFV	-0.871	0.440	3.910	0.048	0.419	0.117	0.992

BUN: blood urea nitrogen, EDFV: end-diastolic flow velocity.

improve glomerular high resistance. Additionally, the comparison of the incidence of adverse reactions in the two groups showed that the additional bumetanide did not significantly increase the incidence of adverse reactions in patients, so it was safe. Through multivariate analysis, we found that older age, higher post-treatment BUN and lower post-treatment EDFV were independent risk factors for unfavorable prognosis. Damaged renal microvessels in patients will successively lead to changes in renal hemodynamics. As the situation worsens, the renal function will also deteriorate [29]. This suggests that in the course of treatment, more attention should be paid to the prognosis of patients based on the renal function and renal blood flow indexes.

This study still has areas that can be inproved. First, we failed to observe the specific effect of the treatment scheme on the pathological manifestations of the kidney, nor did we explore the specific mechanism of valsartan combined with bumetanide on the inflammation and renal function of CGN patients. Therefore, we hope to conduct in-vitro and animal experiments in the future to further explore and prove our findings. Moreover, elderly patients usually suffer multiple diseases, so we hope more inclusive samples can be included in later studies to verify the efficacy and safety.

To sum up, bumetanide tablets combined with valsartan is substantially effective in the treatment of elderly patients with CGN. This combined method can substantially improve the renal function and hemodynamics of the patients, so it has a high clinical application value in the future.

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Disclosure of conflict of interest

None.

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