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Research article

# Clinical efficacy of beraprost sodium in treating chronic kidney disease: A six-month prospective study

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ABSTRACT

*Objective:* To investigate the clinical efficacy of beraprost sodium (BPS) in the treatment of chronic kidney disease (CKD).

*Methods:* In this single-centre, prospective, controlled, single-blind study, 252 patients diagnosed with CKD and treated at the Affiliated Hospital of Xuzhou Medical University were enrolled from September 2018 to June 2021. All participants were randomised into three groups: the control, BPS 40 μg, and BPS 20 μg groups. Both treatment groups were administered conventional therapy for 6 months. Renal function in the three groups was measured and compared 3 and 6 months post-treatment.

*Results:* 1. Renal function in the BPS 20 μg and BPS 40 μg groups was better than that in the control group after 3 and 6 months of treatment. 2. After 3 months of treatment, the levels of serum creatinine ($P = 0.043$), cystatin C ($P = 0.039$), and 24 h urinary total protein ($P = 0.041$) in the BPS 40 μg group were significantly lower than those in the BPS 20 μg group, the eGFR ($P = 0.046$) level was higher than that in the BPS 20 μg group, and the index improvement rate was better than that in the BPS 20 μg group ($P < 0.05$). 3. After 6 months of treatment, the improvement in renal function in the BPS 20 μg group was close to that in the BPS 40 μg group ($P > 0.05$).

*Conclusion:* BPS improved renal function, reduced urinary protein levels, and delayed CKD progression. The clinical efficacy of BPS in the 40 μg group was faster than that in the BPS 20 μg group. The long-term use of BPS is effective in patients with CKD.

## 1. Introduction

Chronic kidney disease (CKD) refers to abnormal kidney structure and function for ≥3 months caused by various reasons, which seriously affects the quality of life of patients and may result in death. Renal replacement therapy is currently the only option that can prolong life when the disease progresses to end-stage renal disease (ESRD), where patients with CKD are physically and mentally exhausted and a substantial economic burden has been placed on the country and family [1]. The National Health and Nutrition Examination Survey showed that the proportion of patients with CKD suffering from ESRD is only 0.6% [2]. With further study of the

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CKD pathogenesis, drugs targeting renal microcirculation function and inhibiting renal interstitial fibrosis are gradually being used to treat CKD. Beraprost sodium (BPS), an oral preparation of prostacyclin analogues, causes in vessel dilation, inhibition of platelet aggregation, and endothelial protection [3,4]. Previously, BPS was primarily used for peripheral arterial occlusive disease and pulmonary arterial hypertension [5,6]. Some studies have shown that BPS delays the progression of CKD [7]. BPS functions in CKD by improving renal microcirculation disturbances, reducing the generation of inflammatory factors, protecting vascular endothelial cells, and preventing interstitial fibrosis development [7,8]. Based on these mechanisms, BPS has renoprotective and anti-inflammatory effects. Several animal experiments and clinical studies have evaluated the effects of BPS on various biomarkers of kidney metabolism in animal models of diabetic kidney disease (DKD) and clinical patients. They showed that BPS improved renal function and reduced urinary protein levels [9–11]. The Chinese Guidelines for the Prevention and Treatment of Diabetic Nephropathy indicate that BPS can be used for the clinical treatment of DKD [12].

Considering the high efficacy of BPS in DKD, it has been gradually used in the clinical treatment of CKD. However, there is no standard dose of BPS for CKD treatment. The recommended dose of BPS in chronic arterial occlusion disease is 40 μg thrice daily (Tid). Chinese clinical studies mostly use this dose to evaluate the efficacy of the treatment of CKD, whereas some studies have reported the efficacy of BPS 20 μg Tid; however, there is a lack of comparative studies on the treatment of CKD with different BPS doses. In addition, the sample size of the existing studies is small, the follow-up time is short, and there is a gap in the study on the correlation between drug dose, treatment duration, and their interaction with CKD efficacy. In addition, foreign large-scale prospective studies have not yet determined the recommended dose of BPS for CKD because the study endpoint has not been reached [13].

Therefore, the present study aimed to address the these problems through a prospective randomized controlled study in a select clinic in the Affiliated Hospital of Xuzhou Medical University with 252 patients with CKD 2–4 period as the research object. Patient were observed to evaluate different doses and a different course of BPS clinical effectiveness and safety in the treatment of CKD to provide a basis for its clinical application.

## 2. Materials and methods

### 2.1. Patients

This prospective study included 252 patients with chronic kidney disease admitted to the Department of Nephrology, Affiliated Hospital of Xuzhou Medical University, from September 2018 to June 2021. The diagnostic criteria of CKD and the stages are divided into stages 1–5 based on the guidelines of the Kidney Disease: Improving Global Outcomes (KDIGO). The inclusion criteria were as follows: (1) Patients with stage 2–4 CKD caused by chronic glomerulonephritis, diabetic nephropathy, hypertensive renal and arteriosclerosis. (2) Age: 18–70 years old; (3) Informed consent to this study has been signed. The exclusion criteria were as follows: (1) Patients who had undergone renal replacement therapy, renal artery stenosis, and bleeding risk diseases; (2) Stress state caused by acute complications such as myocardial infarction, cerebral infarction, tumor history, severe infection. (3) Malignant hypertension or poor blood pressure control (systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg); (4) Taking anti-platelet and anti-coagulant drugs; (5) Incomplete or lost clinical data. This study has been approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University and has been registered for clinical trials Gov. (NCT03682952).

### 2.2. Calculation sample size

According to the pre-experiment results, the autocorrelation coefficient between adjacent measurement points is 0.7. $\alpha = 0.05$ (two-sided Test), degree of confidence $= 1\text{-}\beta = 0.9$, and the three groups' sample size ratio was set at 1:1:1. The menu of "Repeated Measures Analysis" of PASS 15 software, Geisser-greenhouse F Test, was used. According to Scr and eGFR, 44 cases and 71 cases were needed in each group. The allowable rate of loss to follow-up in this study was 10%, and at least 49 cases and 79 cases were required in each group, which can ensure the scientific design of the study.

### 2.3. Grouping and intervention

The control group received conventional treatments such as antihypertensive, lipid-lowering, hypoglycaemic, and ShenYan tablets for kidney protection, and symptomatic support treatments such as iron supplementation, sodium bicarbonate, and anti-infection based on the condition of each patient. The BPS (National Drug Standard: H20083688) 20 μg group, had 20 μg of BPS administered Tid. The BPS 40 μg group was treated with BPS based on conventional treatment for 40 μg Tid. All patients in each group were treated for 6 months.

### 2.4. Blinding

This study was a single-blind study, and the patients were aware of the dose of beraprost sodium. The data collectors were blinded to patient allocation at both groups and time-point.

### 2.5. Baseline information

After enrolment, the baseline data of patients were collected, such as age, sex, medical history, and the course of CKD, body mass

index, history of hypertension and diabetes, types of antihypertensive drugs, SGLT2-i, bicarbonate, primary causes, systolic blood pressure, diastolic blood pressure, and the CKD stage. Relevant records were made and the data were analysed to determine whether there were any variations in baseline information.

### 2.6. Laboratory measurements

The following biochemical parameters were measured in all patients: serum creatinine (Scr), estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), 24-h urinary protein, cystatin C (CysC), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), D-dimer (D-Di), and platelet count (PLT). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration 2-level race equation. The above indices were measured and recorded in the laboratory department of our hospital before treatment and at 3 and 6 months after treatment. We statistically analysed the changing trend of the above indices of patients with different treatment schemes with treatment time and recorded whether the difference in drug dose and treatment time impacted the improvement of patients with CKD. We set a greater than 10% rise in eGFR after treatment as effective and less than 10% or a fall in eGFR as ineffective treatment. Drug efficacy was further assessed by calculating the number needed to treat (NNT).

### 2.7. Adverse event

The adverse drug reactions of patients in each group during treatment included dizziness, headache, facial flushing, bleeding, palpitations, and gastrointestinal reactions. Patients were asked about the degree of adverse reaction symptoms and whether they could tolerate them. If they could be tolerated, treatment was continued. Otherwise, the drug was discontinued, and the patient was withdrawn from the study.

### 2.8. Statistical analysis

SPSS software was used for the statistical analysis of the data. Data consistent with normal distribution were expressed in the form of mean ± standard deviation. Measurement data at different time points between groups were compared using a two-factor repeated-measures analysis of variance. The statistical results referred to the sphericity hypothesis in the intrasubjective effect test when Mauchly's sphericity test was performed. When the Mauchly sphericity test was not performed, the statistical results were based on Pillai's locus in the multivariate test, and the least significant difference method was used for pial comparison. M (P25, P75) was used for data that did not conform to a normal distribution, and the Kruskal-Wallis test was used to compare groups. Statistical data were expressed as number of cases or percentages (%). $\chi^2$ Test or Fisher's exact test was used to compare differences between groups. Statistical significance was set at $P < 0.05$.

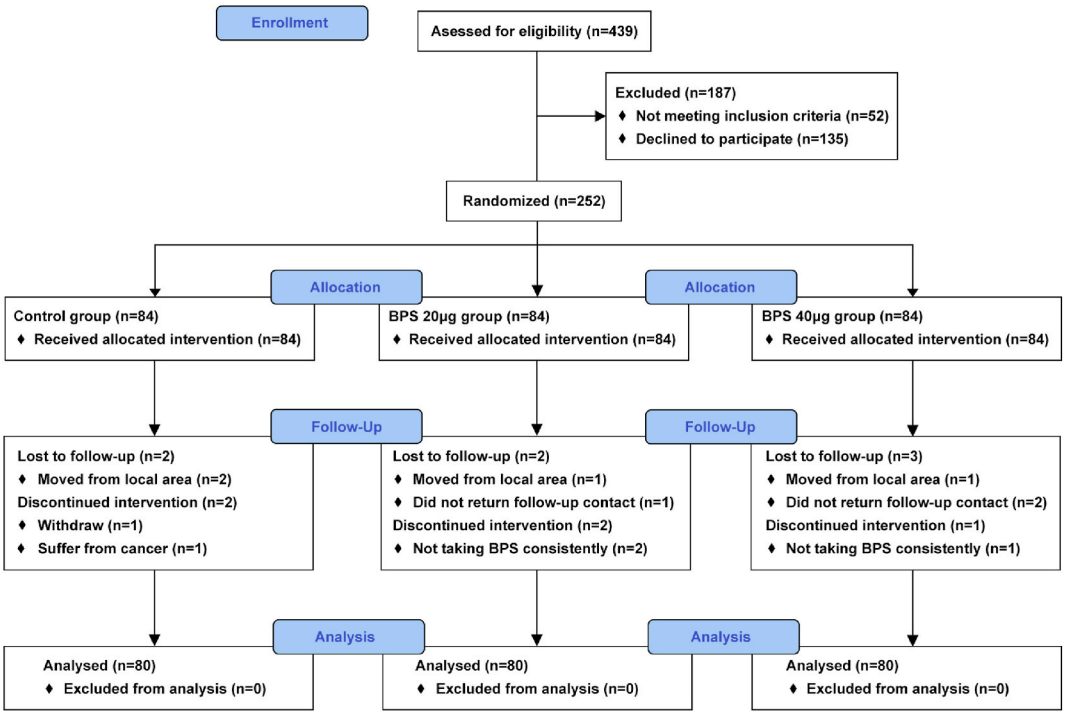


**Fig. 1.** Participant flow diagram of the study design.

## 3. Results

### 3.1. Patient baseline characteristics

A total of 252 patients with stage 2–4 CKD were included in this study, with 84 patients in each group. In the control group, two patients were lost to follow-up: one voluntarily asked to withdraw from the group, and the other had a new malignant tumour. In the BPS 20 μg group, two patients were lost to follow-up, and two others did not agree to taking BPS. In the BPS 40 μg group, three patients were lost to follow-up, and one did not agree to taking BPS. Finally, 80 patients from each group were included in this study. A flowchart of the study is shown in Fig. 1. There were 44 males (55.00%) and 36 females (45.00%) in the control group; the average age was 48.05 ± 9.87 years. There were 37 males (46.25%) and 43 females (53.75%) in the BPS 20 μg group; the average age was 50.50 ± 10.51 years. There were 42 males (52.50%) and 38 females (47.50%) in the BPS 40 μg group; the average age was 51.15 ± 10.22 years. Baseline characteristics were well balanced among the three groups. Both test groups showed no statistically significant differences in sex, age, BMI, disease duration, history of hypertension, and diabetes, blood pressure, antihypertensive drugs, SGLT2-i, CKD stage, primary kidney disease, bicarbonate, or mean eGFR and UTP among the three groups (all $P > 0.05$)—indicating comparability. The baseline characteristics of both test groups are presented in Table 1.

### 3.2. Comparison of renal function indexes between intra-groups

The intra-group comparison showed that the renal function indices of patients in both test groups improved after treatment compared with before treatment. Specifically, Scr, BUN, and UTP levels decreased 3 months after treatment in the control group, whereas eGFR increased, with a statistically significant difference ($P < 0.05$). After 6 months of treatment, Scr and CysC levels decreased and eGFR increased compared with those in the control group before treatment. There was no significant difference in the improvement in renal function between 3 and 6 months in the control group. Scr, UTP, and CysC levels in the BPS 20 μg group were lower than before 3 and 6 months of treatment, whereas the eGFR level was higher than before (all $P < 0.01$). With an increase in treatment duration, the above indicators showed statistically significant differences between 3 and 6 months ($P < 0.01$), except for BUN. In the BPS 40 μg group, Scr, BUN, UTP, and CysC levels at 3 and 6 months of treatment were significantly lower than before, whereas the eGFR level was significantly higher than before, with statistically significant differences ($P < 0.05$). Scr and CysC levels at 6 months were significantly lower than those at 3 months, whereas the eGFR level was significantly higher than that at 3 months ($P < 0.05$). The statistical results of the renal function indices in the three groups before and after treatment are shown in Table 2. Changes in eGFR which respectively estimated using Scr, CysC, and combined Scr-CysC and UTP levels among the three groups are shown in

**Table 1**
Baseline characteristics by study group [n (%), $\bar{x} \pm s$].

| Variables | control group (n = 80) | BPS 20 μg group (n = 80) | BPS 40 μg group (n = 80) | $\chi^2$/H/F | P |
|---|---|---|---|---|---|
| Gender | | | | | |
| Men, n (%) | 44 (55.00) | 37 (46.25) | 42 (52.50) | 1.301 | 0.522 |
| Women, n (%) | 36 (45.00) | 43 (53.75) | 38 (47.50) | | |
| Age, years | 48.05 ± 9.87 | 50.50 ± 10.51 | 51.15 ± 10.22 | 2.027 | 0.134 |
| Disease duration, months | 31.50 (23.00, 48.00) | 36.00 (30.00, 50.00) | 38.50 (27.75, 43.00) | 1.534 | 0.464 |
| BMI | 22.93 ± 2.71 | 23.27 ± 2.79 | 23.07 ± 2.45 | 0.342 | 0.711 |
| Hypertension, n (%) | 60 (75.00) | 57 (71.25) | 63 (78.75) | 1.200 | 0.549 |
| Diabetes, n (%) | 31 (38.75) | 35 (43.75) | 30 (37.50) | 0.729 | 0.694 |
| SBP, mmHg | 131.61 ± 5.66 | 130.91 ± 5.42 | 131.14 ± 6.02 | 0.310 | 0.733 |
| DBP, mmHg | 82.44 ± 4.75 | 80.96 ± 4.86 | 82.11 ± 5.12 | 1.965 | 0.142 |
| Antihypertensive drugs | | | | | |
| ACEI/ARB, n (%) | 56 (70.00) | 50 (62.50) | 53 (66.25) | 1.006 | 0.605 |
| CCB, n (%) | 9 (11.25) | 11 (13.75) | 14 (17.50) | 1.302 | 0.521 |
| Others, n (%) | 4 (5.00) | 3 (3.75) | 3 (3.75) | 0.310 | 1.000 |
| SGLT2-i, n (%) | 10 (12.5) | 13 (16.25) | 8 (10.00) | 1.408 | 0.495 |
| Primary cause of disease, n (%) | | | | | |
| Chronic glomerulonephritis | 33 (41.25) | 28 (35.00) | 35 (43.75) | 3.647 | 0.724 |
| Diabetic nephropathy | 28 (35.00) | 31 (38.75) | 24 (30.00) | | |
| Hypertensive nephropathy | 12 (15.00) | 16 (20.00) | 12 (15.00) | | |
| Other | 7 (8.75) | 5 (6.25) | 9 (11.25) | | |
| CKD stage, n (%) | | | | | |
| G2 | 22 (27.50) | 23 (28.75) | 19 (23.75) | 1.673 | 0.796 |
| G3 | 45 (56.25) | 48 (60.00) | 47 (58.75) | | |
| G4 | 13 (16.25) | 9 (11.25) | 14 (17.50) | | |
| $HCO^{3-}$, mmol/L | 22.63 ± 3.50 | 21.77 ± 3.41 | 22.42 ± 3.67 | 1.292 | 0.277 |
| eGFR, ml/(min·1.73m$^2$) | 43.26 ± 13.68 | 42.24 ± 13.14 | 42.90 ± 12.35 | 0.125 | 0.882 |
| UTP, g·24h$^{-1}$ | 1.48 ± 0.41 | 1.43 ± 0.33 | 1.45 ± 0.37 | 0.367 | 0.693 |

BMI: body mass index, BMI = weight(kg)/height$^2$(m$^2$); ACEI: Angiotensin-Converting Enzyme Inhibitors; ARB: angiotensin receptor blocker; CCB: calcium channel blocker. Continuous variable results in normal distribution are expressed as the means ± SD; continuous variable results in non-normal distribution are expressed as median (interquartile range).

Figs. 2 and 3, respectively.

After 3 and 6 months of treatment, Scr, UTP, and CysC levels were lower, and the eGFR level was higher than before treatment in the BPS 20 μg group (all $P < 0.01$). With an increase in the duration of therapy, there was a significant difference in the above indices after 6 months of treatment compared with that after 3 months of treatment ($P < 0.01$). After 3 and 6 months of treatment, Scr, BUN, UTP, and CysC levels were significantly lower than before treatment, and the eGFR level was significantly higher than that before treatment in the BPS 40 μg group ($P < 0.05$). In the BPS 40 μg group, Scr and CysC levels were lower 3 months after treatment compared to 6 months of treatment, and the eGFR level was higher after 6 months than after 3 months ($P < 0.05$).

Inter-groups comparison showed that Scr, UTP, and CysC levels in the BPS 20 μg and BPS 40 μg groups were lower than those in the control group at 3 and 6 months after treatment, and the eGFR level was higher than that in the control group. The difference was statistically significant ($P < 0.05$). The degree of Scr, UTP, and CysC level reduction in the BPS 40 μg group was more significant at 3 months after treatment than at 6 months after treatment; the difference was statistically significant in the BPS 20 μg group ($P < 0.05$), whereas there was no statistically significant difference in the two groups at 6 months after treatment ($P > 0.05$). The statistical results of BUN showed that different treatment methods had no significant effect on BUN levels, and there was no statistically significant difference among all groups at the same time point ($P > 0.05$).

NNT was further assessed for the therapeutic efficacy of BPS, and it was found that after 3 months of treatment, the NNT of BPS 20 μg group was 3.478 with 95% CI (2.296, 7.173), and the NNT of BPS 40 μg group was 2.286, 95% CI (1.736, 3.346) reflecting fine effect of improving eGFR for CKD patients. After 6 months of treatment, the BPS has also shown good efficacy. However, using the BPS 20 μg group as a control, at 3 months, the NNT of the BPS 40 μg group was 6.667, 95% CI (3.428, 121.228) indicating a better therapeutic effect than that of the BPS 20 μg group. After 6 months of treatment, the NNT of BPS 40 μg group was 26.667, 95% CI included 0, indicating that there was no significant difference in efficacy between the two groups, which was consistent with the above results of renal function related indexes (Table 3).

### 3.3. Comparison of coagulation function and platelets between groups

After 3 and 6 months of treatment, FIB and D-Di levels in the BPS 20 and 40 μg groups decreased significantly compared with those before treatment. FIB and D-Di levels at 6 months of treatment were lower than those at 3 months of treatment; there was a statistically significant difference in the BPS 20 μg group ($P < 0.01$). In the BPS 40 μg group, the D-Di level at 6 months of treatment was significantly lower than that at 3 months ($P < 0.01$), whereas no significant difference existed for the FIB level ($P > 0.05$). The inter-groups comparison showed that FIB and D-Di levels in the BPS 20 μg and BPS 40 μg groups were lower than those in the control group after 3 and 6 months of treatment. Compared with other groups, the FIB level in the BPS 40 μg group was significantly decreased at 3 months of treatment ($P < 0.05$). PT, APTT, and PLT levels in the BPS 20 and 40 μg groups showed no significant differences before and after treatment, whereas coagulation function and PLT in the control group showed no significant differences ($P > 0.05$) (Table 4).

**Table 2**
Comparison of renal function among three groups at a different time ($\overline{x} \pm s$, n = 80).

| | Scr (μmol/L) | | | eGFR [ ml/(min·1.73m$^2$)] | | |
|---|---|---|---|---|---|---|
| | Prior treatment | After 3 months | After 6 months | Prior treatment | After 3 months | After 6 months |
| Control group | 150.94 ± 32.60 | 146.85 ± 26.81$^{c}$ | 146.31 ± 29.15$^{c}$ | 43.26 ± 13.68 | 44.13 ± 12.27 | 45.02 ± 13.34$^{cd}$ |
| BPS 20 μg group | 148.65 ± 31.91 | 136.25 ± 23.23$^{ac}$ | 127.12 ± 24.85$^{acd}$ | 42.24 ± 13.14 | 47.90 ± 11.11$^{ac}$ | 51.22 ± 12.60$^{acd}$ |
| BPS 40 μg group | 150.19 ± 28.53 | 128.28 ± 20.86$^{abc}$ | 123.95 ± 21.78$^{acd}$ | 42.90 ± 12.35 | 51.68 ± 12.14$^{abc}$ | 53.69 ± 13.20$^{acd}$ |
| Methods | F = 6.218 P = 0.002 | | | F = 3.661 P = 0.027 | | |
| Time | F = 171.601 P < 0.001 | | | F = 161.124 P < 0.001 | | |
| Methods*Time | F = 31.000 P < 0.001 | | | F = 24.275 P < 0.001 | | |

| | BUN (mmol/L) | | | UTP (g·24h$^{-1}$) | | | CysC (mg/L) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Prior treatment | After 3 months | After 6 months | Prior treatment | After 3 months | After 6 months | Prior treatment | After 3 months | After 6 months |
| Control group | 9.39 ± 1.72 | 9.12 ± 1.52$^{c}$ | 9.27 ± 1.58 | 1.48 ± 0.41 | 1.37 ± 0.30$^{c}$ | 1.41 ± 0.27 | 2.32 ± 0.62 | 2.24 ± 0.67 | 2.19 ± 0.64$^{c}$ |
| BPS 20 μg group | 9.41 ± 2.21 | 9.18 ± 1.73 | 9.14 ± 1.51$^{c}$ | 1.43 ± 0.33 | 1.06 ± 0.25$^{ac}$ | 0.97 ± 0.21$^{acd}$ | 2.29 ± 0.54 | 2.03 ± 0.47$^{ac}$ | 1.82 ± 0.44$^{acd}$ |
| BPS 40 μg group | 9.51 ± 2.23 | 9.03 ± 1.89$^{c}$ | 8.98 ± 1.66$^{c}$ | 1.45 ± 0.37 | 0.98 ± 0.23$^{abc}$ | 0.93 ± 0.19$^{ac}$ | 2.38 ± 0.43 | 1.85 ± 0.48$^{abc}$ | 1.76 ± 0.37$^{acd}$ |
| Methods | F = 0.059 P = 0.943 | | | F = 38.278 P < 0.001 | | | F = 6.568 P = 0.002 | | |
| Time | F = 10.098 P < 0.001 | | | F = 139.693 P < 0.001 | | | F = 95.088 P < 0.001 | | |
| Methods*Time | F = 1.472 P = 0.210 | | | F = 17.740 P < 0.001 | | | F = 15.160 P < 0.001 | | |

Scr: serum creatinine; eGFR: estimated glomerular filtration rate; BUN: blood urea nitrogen; UTP：24-h urinary protein; CysC: cystatin C.
At the same time point, a: compared with the control group, $P < 0.05$; b: Compared with the BPS 20 μg group, $P < 0.05$. Under the same treatment condition, c: compared with before treatment, $P < 0.05$; d: Compared with 3 months, $P < 0.05$.

**Table 3**
Number needed to treat (NNT) assessing drug efficacy [n (%)].

| | After 3 months | | NNT (95% CI) | After 6 months | | NNT (95% CI) |
|---|---|---|---|---|---|---|
| | Effective | Ineffective | | Effective | Ineffective | |
| Control group | 26 (32.5) | 54 (67.5) | | 32 (40.0) | 48 (60.0) | |
| BPS 20 μg group | 49 (61.25) | 31 (38.75) | 3.478 (2.296, 7.173) | 60 (75.0) | 20 (25.0) | 2.857 (2.027, 4.837) |
| BPS 40 μg group | 61 (76.25) | 19 (23.75) | 2.286 (1.736, 3.346)[a]<br>6.667 (3.428, 121.228)[b] | 63 (78.75) | 17 (21.25) | 2.581 (1.896, 4.038)[a]<br>26.667[c] |

a: compared with control group; b: compared with BPS 20 μg group; c: compared with BPS 20 μg group, 95% CI contains 0.

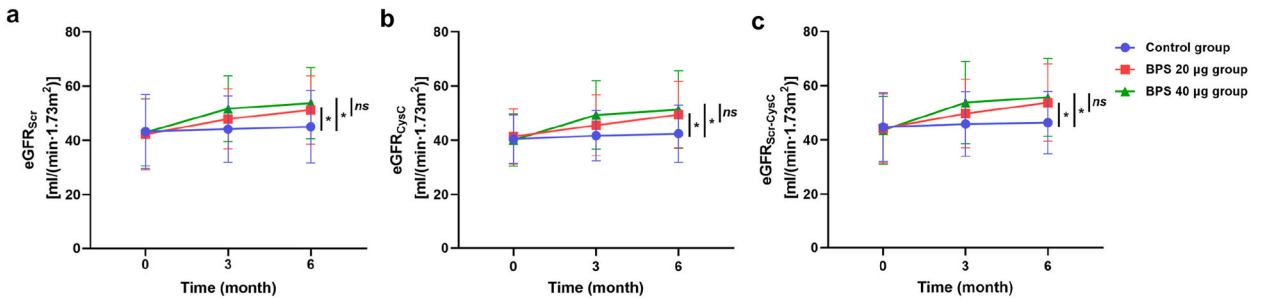


**Fig. 2.** The changes of eGFR level (mean ± SD) in patients among the control group (blue), BPS 20 μg (red) and BPS 40 μg (green). Estimated using Scr (a), CysC (b), and combined Scr-CysC (c), respectively. (*ns* $P > 0.05$, *$P < 0.05$).

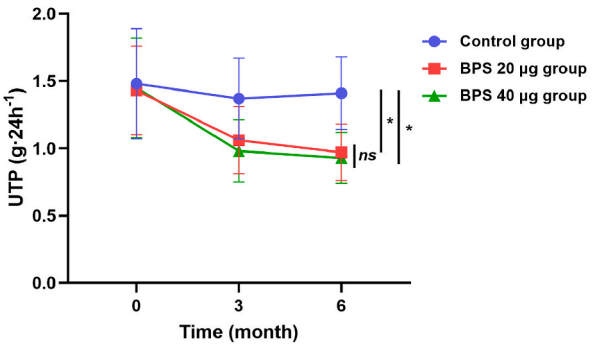


**Fig. 3.** The changes of UTP level (mean ± SD) in patients among the control group (blue), BPS 20 μg group (red) and BPS 40 μg group (green). (*ns* $P > 0.05$, *$P < 0.05$).

### *3.4. Comparison of the occurrence of adverse reactions*

During treatment, one case of slight headache, one of palpitations, and two of gastrointestinal discomfort were reported in the control group. Three cases of slight headache, one of facial flushing, one of palpitation, and one of anorexia were reported in the BPS 20 μg group. Three cases of slight headache, one of facial flushing, one of palpitation, and two of gastrointestinal reactions were reported in the BPS 40 μg group. The adverse reactions were well tolerated by all patients with no discontinuation of the drug. There was no significant differences in the incidence of total adverse reactions among the groups ($\chi^2 = 0.886$, $P = 0.642$) (Table 5).

## 4. Discussion

In the present study, we determined that BPS delayed CKD progression. Compared with the conventional treatment of CKD, the addition of BPS can significantly reduce Scr and urinary protein, increase eGFR, and improve the hypercoagulability of patients with CKD. BPS was thus shown to improve renal function in time- and dose-dependent manners. Collectively, BPS has a good clinical application value in CKD.

The kidney is a highly vascularised organ that relies on a rich capillary network to deliver oxygen and nutrients to the renal tubules. Therefore, a rich circulating blood supply is essential to maintain normal renal function. Progressive capillary loss is an attribute of disease progression for CKD [14]. Destruction of the glomerular capillary network, apoptosis of endothelial cells, and continuous hypoxia caused by peritubular capillary injury. These factors lead to oxidative stress, inflammatory cell activation, and release of

**Table 4**
Comparison of coagulation indicators among three groups at different times($\bar{x} \pm s$, n = 80).

| | PT ( s ) | | | APTT ( s ) | | | PLT ( $\times 10^9$/L ) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Prior treatment | After 3 months | After 6 months | Prior treatment | After 3 months | After 6 months | Prior treatment | After 3 months | After 6 months |
| Control group | 10.22 ± 1.30 | 10.28 ± 1.36 | 10.35 ± 1.26 | 28.49 ± 3.74 | 29.24 ± 4.10 | 29.14 ± 3.33 | 230.55 ± 40.25 | 231.40 ± 44.23 | 228.55 ± 33.12 |
| BPS 20 μg group | 10.32 ± 1.19 | 10.30 ± 1.15 | 10.37 ± 1.10 | 29.52 ± 3.80 | 29.54 ± 3.49 | 30.01 ± 4.08 | 236.85 ± 39.36 | 231.05 ± 40.10 | 232.10 ± 34.89 |
| BPS 40 μg group | 10.31 ± 1.22 | 10.43 ± 1.31 | 10.41 ± 1.28 | 29.09 ± 2.89 | 28.93 ± 4.04 | 29.47 ± 3.56 | 232.00 ± 45.96 | 228.50 ± 37.50 | 231.75 ± 37.84 |
| Methods | F = 0.140 P = 0.869 | | | F = 2.625 P = 0.075 | | | F = 0.170 P = 0.844 | | |
| Time | F = 2.117 P = 0.123 | | | F = 1.119 P = 0.327 | | | F = 1.373 P = 0.255 | | |
| Methods* time | F = 0.739 P = 0.565 | | | F = 0.349 P = 0.845 | | | F = 1.042 P = 0.385 | | |

| | FIB ( g/L ) | | | D-Di ( mg/L ) | | |
|---|---|---|---|---|---|---|
| | Prior treatment | After 3 months | After 6 months | Prior treatment | After 3 months | After 6 months |
| Control group | 3.93 ± 1.14 | 3.78 ± 1.03 | 3.80 ± 1.19 | 1.77 ± 0.49 | 1.82 ± 0.38 | 1.75 ± 0.37 |
| BPS 20 μg group | 3.87 ± 1.31 | 3.21 ± 1.01[ac] | 2.76 ± 0.86[acd] | 1.83 ± 0.68 | 1.49 ± 0.35[ac] | 1.28 ± 0.32[acd] |
| BPS 40 μg group | 3.83 ± 1.29 | 2.87 ± 1.01[abc] | 2.74 ± 0.73[ac] | 1.75 ± 0.37 | 1.40 ± 0.26[ac] | 1.19 ± 0.38[acd] |
| Methods | F = 11.103 P < 0.001 | | | F = 18.437 P < 0.001 | | |
| Time | F = 86.446 P < 0.001 | | | F = 61.555 P < 0.001 | | |
| Methods*Time | F = 16.893 P < 0.001 | | | F = 12.519 P < 0.001 | | |

APTT: activated partial thromboplastin time; PT: prothrombin time; PLT: platelet count; FIB: fibrinogen; D-Di: D-dimer. At the same time point, a: compared with the control group, $P < 0.05$; b: Compared with the BPS 20 μg group, $P < 0.05$. Under the same treatment condition, c: compared with before treatment, $P < 0.05$; d: Compared with 3 months, $P < 0.05$.

**Table 5**
Comparison of adverse drugs reactions among three groups during treatment (n).

| | Dizziness/Headache | Facial flushing | Palpitation | Gastrointestinal reaction | Adverse reaction |
|---|---|---|---|---|---|
| Control group | 1 | 0 | 1 | 2 | 4 |
| BPS 20 μg group | 3 | 1 | 1 | 1 | 6 |
| BPS 40 μg group | 3 | 1 | 1 | 2 | 7 |
| $\chi^2$ | 1.260 | 1.250 | 0.431 | 0.593 | 0.886 |
| P | 0.706 | 1.000 | 1.000 | 1.000 | 0.642 |

various cytokines. Multiple pathways lead to mesangial cell proliferation, extracellular matrix (ECM) accumulation, and endothelial-mesenchymal cell transformation (EndMT). Finally, the vicious cycle of hypoxic-microcirculation-hypoxia promotes glomerulosclerosis, renal tubular atrophy, and interstitial fibrosis, resulting in microcirculatory failure and deterioration of renal function [15,16].

BPS, an oral prostacyclin ($PGI_2$) analogue, retains the pharmacological effects of vasodilating smooth muscle and anti-platelet aggregation similar to PGI2 and prolongs its half-life in vivo [17]. Previous animal experiments by our research group showed that BPS can improve renal microcirculation in a mouse model of unilateral ureteral obstruction [18]. By repairing damaged peritubular capillaries, reducing the expression of proinflammatory cytokines such as monocyte chemoattractant protein-1 (MCP-1) and interleukin-6, alleviating oxidative stress, and reducing the renal inflammatory response. Therefore, BPS reduces ECM deposition, EndMT, and renal interstitial fibrosis. Fujita et al. [19] suggested that BPS can slow CKD progression by increasing the renal blood flow without glomerular hyperfiltration. In a meta-analysis by Nowrouzi-Sohrabi et al., BPS significantly reduced the Scr, BUN, and CysC levels in patients with diabetic nephropathy. Because of these clinical benefits, BPS has been progressively applied in clinical settings for the treatment of CKD [20].

BPS is a non-renal clearance drug with a low excretion rate and metabolism in its original form. There is no unified standard for drug dosage and treatment course for CKD. A multicentre randomised controlled trial conducted by Koyama et al. determined the recommended dose of the sustained-release dosage form of BPS (TRK-100STP) for patients with CKD in Japan [21]. The research showed that TRK-100STP can potentially prevent renal function decline in patients with CKD but failed to determine the recommended dose for treatment because the study failed to reach the primary endpoint. Therefore, to address this clinical problem, the present study compared and analysed the clinical efficacy of different doses and courses of BPS in treating CKD and evaluated drug safety.

The results of this study showed that different doses of BPS improved renal function in patients with CKD. This result is consistent with those of previous studies. Compared with the control group, BPS decreased the Scr and CysC levels and improved the eGFR level. The improvement was more significant with increasing treatment time. Compared with the BPS 20 μg group, the BPS 40 μg group showed improved renal function after a shorter treatment time and both doses of BPS achieved similar results after 6 months of treatment. Therefore, we hypothesize that BPS improves renal function in time- and dose-dependent manners. A comparison of BUN

levels among the three groups showed no statistically significant differences between the groups at the same treatment time. The results indicated that only treatment time affected BUN levels. However, a clinical trial conducted by Shima et al. showed no significant differences in BUN levels from baseline after 48 weeks of BPS treatment [22]. A possible reason for this is that BUN does not accurately reflect the improvement in renal function in patients. As the end product of protein metabolism in the body, the BUN level is subject to the interference and fluctuation of several extrarenal factors, such as the protein diet [23].

Proteinuria is a potential prognostic marker of CKD as well as an independent risk predictor of CKD progression. Previous studies have suggested that proteinuria results from glomerular filtration barrier or tubulointerstitial injury. However, in recent years, several experimental studies have shown that proteinuria is an indicator of kidney disease and closely related to CKD progression [24,25]. Adding on, aggregated lipoproteins in the glomerular mesangial region, especially low-density lipoprotein (LDL), plays a significant role. More oxidative cytotoxic LDL can form in macrophages and glomerular mesangial cells (GMC), further stimulating MCP-1, platelet-derived growth factor, and other transmitters that promote collagen synthesis and cell proliferation, damage the GMC, increase the formation of the mesangial matrix, and eventually aggravate glomerulosclerosis [26].

In contrast, filtered albumin and immunoglobulin G stimulate the abnormal regulation of the proximal tubular epithelial cell signal pathway. It rapidly and continuously produces reactive oxygen species; activates and releases various inflammatory factors; causes changes in renal tubular cell proliferation, apoptosis, and gene transcription; and induces renal tubule interstitial inflammation and fibrosis [27]. In the present study, both doses of BPS reduced proteinuria in patients. The BPS 40 μg group showed a more significant decline in proteinuria in the short term. These results are consistent with those of previous studies, indicating that BPS can effectively reduce proteinuria in patients with CKD, protect the kidneys, and delay CKD progression.

It is well known that CKD is usually progressive, and hypertension is a risk factor for the progression of CKD and one of the most common complications in CKD patients. In China, about 79.8% of non-dialysis CKD patients have hypertension [28]. Poor blood pressure control not only promotes the progression of CKD, but also leads to myocardial remodelling and increases the risk of cardiovascular events [29]. BPS acts on prostacyclin receptors in vascular smooth muscle cells, inhibiting $Ca^{2+}$ inward flow and acting as a vasodilator, thus regulating blood pressure in patients. Therefore, this may also make BPS one of the reasons for delaying the progression of CKD.

The laboratory test of coagulation function showed no significant changes in PT, APTT, and PLT in each group, but the FIB and D-Di levels in serum were reduced following BPS treatment. The Quality of Kidney Disease Prognosis Initiative reported that patients with CKD stage 2 should reduce their risk of cardiovascular disease while delaying disease progression. Studies have shown that a hypercoagulable state is common in patients with CKD 2–4 [30]. However, a hypercoagulable state plays a role in the complications of CKD, contributes to the occurrence and development of CKD, and significantly increases the risk of cardiovascular events and death in patients with CKD [31]. The results of this study are consistent with those of previous studies [32,33]. BPS can decrease FIB and Di-d levels in patients with CKD. The decrease of FIB and D-Di levels can reduce the formation of micro thrombosis in the glomerulus and the deposition of fibrin in renal tissue. Therefore, the remaining nephrons are protected and the incidence of thrombosis and cardiovascular events is reduced in patients with CKD to improve prognosis.

A few common minor adverse drug reactions occurred in each treatment group during the observation period, which were well-tolerated by all patients and did not require discontinuation. There were four, six, and seven cases in the control group, BPS 20 μg group, and BPS 40 μg group, respectively. There were no statistically significant differences in the incidence of adverse drug reactions among the three groups, indicating that BPS is safe for CKD treatment.

However, this study has some limitations. First, we observed the changes in platelet number in each group according to the inhibition of platelet aggregation by BPS but did not test platelet function. Second, this study is more convincing if the improvement in microcirculation can be evaluated using new technologies, such as blood oxygen level-dependent MRI. Furthermore, the inclusion of this study is limited to Chinese people, which somewhat weakens the impact of this study. Finally, as this study is a single-centre prospective study with a short follow-up period, the results may have some limitations. Soon, we expect more large-scale, multicentre, randomised controlled studies to help standardise the application of BPS in the clinical treatment of CKD and for more targeted measures to be implemented to delay CKD progression while reducing the economic pressure on patients.

In conclusion, BPS can safely and effectively improve renal function, reduce FIB and D-Di levels in patients with CKD, and improve the hypercoagulable state of patients with CKD. BPS 40 μg Tid works faster than BPS 20 μg Tid, indicating dose-dependent effects. There is a correlation between short-term treatment effects and drug dose. Long-term administration of BPS resulted in similar improvements in renal function and patient's quality of life. Therefore, BPS shows promising clinical applications in CKD treatment.

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## Data availability statement

Data will be made available on request.

## Ethical approval and consent to participate

This study was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2018-KL034-01). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee. All the enrolled patients signed an informed consent form.

## CRediT authorship contribution statement

**Chen Sun:** Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Xin Wu:** Data curation, Formal analysis. **Xin Zhang:** Data curation, Formal analysis. **Shulin Li:** Funding acquisition, Resources. **Ruoyu Jia:** Data curation, Formal analysis. **Dong Sun:** Funding acquisition, Project administration, Resources, Supervision.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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