Urinary and Renal Research (2022) Volume 3 Issue 2, *pp.*1–6.

doi:10.54517/urr.v2i2.2096

Original Research Article

Effects of alprostadil combined with levocarnitine on renal function and inf1ammatory factors in patients with ESDN

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ABSTRACT

Objective To explore the effects of alprostadil combined with levocarnitine on renal function and serum levels of toll-like receptor-4 (TLR-4), interleukin-18 (IL-18) and tumor necrosis factor-α (TNF-α) in patients with end-stage diabetic nephropathy (ESDN). Methods 88 cases of patients with ESDN admitted between January 2015 and January 2018 were divided into observation group (*n*=44) and control group (*n*=44) Alprostadil was applied to both groups, and the observation group was combined with levocarnitine. renal function [serum creatinine (SCr), urea nitrogen (BUN), glomerular filtration rate (eGFR)], inflammatory factors (TLR-4, IL-18, TNF-α) and blood biochemical indicators [hemoglobin(Hb), serum albumin(ALB), cholesterol(TC)] were evaluated before treatment and after 4 weeks of treatment. The incidence rate of dialysis adverse reactions was recorded in the 2 groups. After 4 weeks of treatment, the levels of SCr and BUN in the 2 groups were lower than those before treatment (P<0.05), and the decrease in observation group was greater than that in control group (P<0.05). There was no significant difference in the eGFR within-groups before and after treatment and between groups(P>0.05). After 4 weeks of treatment, the levels of TLR-4, IL-18 and TNF-α in the 2 groups were lower than those before treatment (P<0.05), and the decrease in observation group was greater than that in control group (P<0.05). After 4 weeks of treatment, the levels of Hb and ALB in the 2 groups were higher than those before treatment (P<0.05) while the TC level in the 2 groups was lower than that before treatment (P<0.05), and the changes in observation group were greater than those in control group (P<0.05). The incidence rate of adverse reactions in observation group was lower than in control group (P<0.05). Conclusions Alprostadil combined with levocarnitine is beneficial to reduce the levels of inflammatory factors, protect patients' renal function, Alprostadil combined with levocarnitine is beneficial to reduce the levels of inflammatory factors, protect patients' renal function, and reduce the risk of adverse reactions.

Keywords: End-stage diabetic nephropathy; Alprostadil; Levocarnitine; Renal function

Among all causes of end-stage renal disease, end-stage diabetic nephropathy (ESDN) has the

second highest incidence, after glomerulonephritis [1]. The incidence of infectious diseases and malignant tumors in patients on hemodialysis is on the rise, and hemodialysis is beneficial for improving patients' clinical symptoms and prolonging their survival, but it cannot completely improve their immune function [3]. The current intervention drugs for diabetic nephropathy (DN) patients include immunosuppressants, thiazolidinediones and statins [4]. Levocanidine is a water-soluble small molecule amino acid salt that inhibits the activation of monocytes in peripheral blood, has anti-inflammatory and antioxidant effects, and can effectively regulate the blood pressure and nutritional status of patients [5]. prostilbestrol has good anticoagulant effects and helps to protect the renal function of ESDN patients, while levocanidine may regulate the immune function and inflammatory factor levels of ESDN patients in multiple ways. It has been suggested that levetiracetam has been shown to enhance cellular immune function in patients on maintenance hemodialysis for end-stage renal disease [6] [7-8], but on the one hand, the combination of levetiracetam and prostaglandin has been less studied, and on the other hand, similar studies have focused on patients with DN but less on patients with ESDN. In this study, 88 patients with ESDN were included to investigate the effect of prostaglandin in combination with levetiracetam in the treatment of ESDN, and to provide ideas for better adjuvant drug regimen for ESDN.

1. Data and Methods

1.1. General Information

Eighty-eight patients with ESDN admitted between January 2015 and January 2018 were included in the study. Inclusion criteria: met the diagnostic criteria for ESDN [9]; age >18 years; no recent use of immunomodulators; all on regular dialysis for more than 6 months; expected survival of more than 6 months; all patients gave informed consent and signed the informed consent form; approved by the ethics committee of our hospital. Exclusion criteria: severe heart and liver dysfunction, malignant tumors; renal failure due to systemic lupus erythematosus, vasculitis, etc.; recent infection, surgery, trauma; levocanidine use within six months; clear contraindications to this group; failure to complete 4 weeks of treatment for various reasons. The differences were not statistically significant (P>0.05), see Table 1.

Table 1. Comparison of general data in the 2 groups $[n(\%), \bar{x} \pm s]$

Group	n	Male to female ratio	Age (years)	Body weight(kg)	Mean arterial pressure (mmHg)	Average urine volume (mL)
Observation group	44	25/19	57.06±9.01	61.22±5.91	107.76±11.80	1022.52±255.74
Control group	44	26/18	58.07±7.05	60.40±6.54	110.65±10.14	1010.64±264.76
χ^2/t	-	0.047	0.586	0.617	1.232	0.214
P	-	0.829	0.560	0.539	0.221	0.831

1 mmHg = 0.133 kPa

1.2. Treatment method

In both groups, 1 mL of prostaglandin (manufacturer: Beijing TED Pharmaceutical Co., Ltd., specification: 1 mL: 5 μg, approval number: Guodianzhi H10980023) was dissolved in 10 mL of 0.9% saline and pumped slowly, qd, Ltd., specification: 5 mL:1 g, approval No.: State Drug Administration H20113429) 5 mL of the drug was added to 250 mL of 0.9% saline intravenously, qd, and both groups were treated continuously for 4 weeks.

1.3. Evaluation Methodology

Peripheral venous blood was collected before and after 4 weeks of treatment, and serum creatinine (SCr) and urea nitrogen (BUN) were measured by enzyme-linked immunosorbent assay (ELISA), and chronic kidney disease epidemiology (CKD) was used to estimate glomerular filtration rate (eGFR). The CKD‐EPI formula was used to estimate the glomerular filtration rate (eGFR); the Toll‐likereceptor‐4 (TLR4), interleukin‐18 (IL18),

interferon -18 (IL18), and interleukin -18 (IL18) were measured by ELISA. IL-18, tumor necrosis factor -α (TNF-α), total cholesterol (TC), and hemoglobin (Hb) and albumin (ALB) were measured by radioimmunoassay.)

1.4. Observed indicators

The renal function (SCr, BUN, GFR), inflammatory factors (TLR - 4, IL - 18, TNF - α) and blood biochemical indexes (Hb, ALB, TC) of the two groups were evaluated before and after 4 weeks of treatment, and the incidence of dialysis adverse effects in the two groups was recorded.

1.5 Statistical methods

SPSS 19.0 statistical software was used for data analysis, and the measured data were expressed as mean ± standard deviation (x ± s) by t-test, and the count data were expressed as n(%) by c2 test or Fisher's exact probability test, and P<0.05 indicated that the differences were statistically significant.

2. Results

2.1. Comparison of renal function between the 2 groups

After 4 weeks of treatment, the SCr and BUN levels in both groups were lower than before treatment (P<0.05), and the decrease in the observation group was greater than that in the control group (P<0.05); the differences were not statistically significant (P>0.05) between the two groups before and after treatment and between groups in terms of eGFR, see Table 2.

Table 2. Comparison of renal function in the 2 groups

Group		*n*	SCr(μmol/L)	BUN(mmol/L)	eGFR[mL/(min×1.73m2)
Observation group	Before treatment	44	826.59±82.60	29.42±9.42	11.17±1.45
	After 4 weeks of treatment	44	669.12±138.15[ab]	22.17±6.75[ab]	10.64±1.08
t	-	-	6.489	4.150	1.944
P	-	-	0.000	0.000	0.055
Control group	Before treatment	44	828.87±83.52	29.65±9.90	11.08±1.86
	After 4 weeks of treatment	44	753.30±129.54[b]	25.45±7.18[b]	10.43±1.16
t	-	-	3.252	2.278	1.967
P	-	-	0.002	0.025	0.052

Compared with the control group in the same period, aP<0.05; compared with the same group before treatment, bP<0.05.

Table 3. Comparison of levels of inflammatory factors in the 2 groups($\bar{x} \pm s$)

Group		*n*	TLR-4(pg/mL)	IL-18(ng/mL)	TNF-α(pg/mL)
Observation group	Before treatment	44	6.53±0.93	156.52±23.37	28.41±6.74
	After 4 weeks of treatment	44	4.89±0.84[ab]	116.92±19.62[ab]	14.24±4.91[ab]
t	-	-	8.681	8.608	11.272
P	-	-	0.000	0.000	0.000
Control group	Before treatment	44	6.49±0.92	157.70±28.56	28.75±6.14
	After 4 weeks of treatment	44	5.53±0.85[b]	132.46±16.06[b]	19.81±5.83[b]
t	-	-	5.084	5.110	7.004
P	-	-	0.000	0.000	0.000

Compared with the control group in the same period, aP<0.05; compared with the same group before treatment, bP<0.05.

Table 4. Comparison of blood biochemical indicators in the 2 groups(x ± s)

Group		*n*	Hb(g/L)	ALB(g/L)	TC(mmol/L)
Observation group	Before treatment	44	64.57±13.99	25.15±5.73.	5.86±1.40
	After 4 weeks of treatment	44	94.25±14.35ab	41.09±5.55ab	3.25±1.08ab
t	-	-	9.824	13.255	9.791
P	-	-	0.000	0.000	0.000
Control group	Before treatment	44	65.19±12.87	25.73±5.61	5.64±1.36
	After 4 weeks of treatment	44	86.57.±16.09b	34.82±4.85b	4.50±1.28b
t	-	-	6.883	8.131	4.049
P	-	-	0.000	0.000	0.000

Compared with the control group in the same period, aP<0.05; compared with the same group before treatment, bP<0.05.

2.2. Comparison of inflammatory factors in 2 groups

After 4 weeks of treatment, the levels of TLR-4, IL-18 and TNF-α in both groups were lower than those before treatment (P<0.05), and the decrease in the observation group was greater than that in the control group (P<0.05), as shown in Table 3.

2.3. Comparison of blood biochemical index levels between the 2 groups

After 4 weeks of treatment, the levels of Hb and ALB in both groups were higher than those before treatment (P<0.05), and the levels of TC in both groups were lower than those before treatment (P<0.05), and the changes in the observation group were greater than those in the control group (P<0.05), see Table 4.

2.4. Comparison of the incidence of adverse dialysis reactions between the 2 groups

In the observation group, there were 1 case of bleeding, 2 cases of hypotension and 2 cases of infection, with an overall incidence of 11.36% (5/44); in the control group, there were 2 cases of bleeding, 6 cases of infection and 6 cases of hypotension, with an overall incidence of 31.82% (14/44).

3. Discussion

Prostaglandin E, the main component of prostaglandin, can improve the coagulation status and renal hemodynamics of the body, which can help to protect renal function. The long-term use of hemodialysis is required to ensure renal function in ESDN, but the plasma and tissue levels of natural levocannabinoids in patients on long-term hemodialysis are significantly reduced, affecting the metabolic and nutritional status of patients [12]. Therefore, in this study, we investigated the effects of the combination of prostaglandin and leucovorin on renal function, inflammatory factors and blood biochemical parameters in patients with ESDN.

The poor prognosis may be related to cardiovascular disease, hemodynamic instability, arteriovenous fistula problems, and increased susceptibility to infection [14]. The stimulation of endotoxin and immune complexes in patients with ESDN activates the macrophage system, which releases various pro-inflammatory factors, resulting in microinflammatory responses [15]. The results showed that high TLR4 expression activated the TLR4 signaling pathway and affected the development of diabetic nephropathy.

The results of this study showed that the levels of TLR-4, IL-18 and TNF-α decreased after treatment, and the decrease in the observation group was significantly greater than that in the control group, which indicates that prostilbestrol combined with leucovorin is beneficial to control the levels of inflammatory factors in the body of ESDN patients. Levocarnitine is a common amino acid, levocarnitine, which is widely present in the body and is an important molecule in the fat oxidation process, and has certain anti-inflammatory and antioxidant effects. In a study by Yu Wu Zhongzhong [19], the addition of levocanidine to conventional

medication was found to be beneficial in improving the nutritional status and microinflammation of patients, which is consistent with the findings of the present study. The study was limited by the sample size and was divided into two groups only.

In patients with end-stage renal disease, the amount of endogenous lecanetine synthesis is significantly reduced due to the low protein diet and the small molecular weight of lecanetine, which can be removed in large quantities during dialysis, resulting in a significant decrease in the concentration of lecanetine in tissues and plasma [21]. On the other hand, it has been reported that lecanidin inhibits the activity of metalloproteinases in the kidney and has a strong inhibitory effect on the pathway of conversion of early glycosylation products to end products, which has a protective effect on renal function [22]. The results of this study also showed that the SCr and BUN levels in the observation group were lower than those in the control group, which is consistent with the above findings. The blood biochemical data also showed that the levels of Hb, ALB and TC were improved in the observation group, which also reduced the risk of cardiovascular disease in patients with ESDN. the incidence of adverse reactions in the observation group was significantly lower than that in the control group during treatment, which was similar to the findings of Huang Juan [24] and others.

In conclusion, the application of prostaglandin combined with levocanidine in ESDN is beneficial to protect the renal function of patients, reduce the level of inflammatory factors in the body, regulate the level of biochemical indicators such as cholesterol, and control the incidence of dialysis adverse effects.

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