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Effect of hyperbaric oxygen combined with alprostadil in the treatment of elderly diabetic nephropathy and effects on serum miR-126 and miR-342 levels

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Abstract: This study aims to investigate the effect of hyperbaric oxygen combined with alprostadil in the treatment of elderly diabetic nephropathy (DN) and its effect on serum miR-126 and miR-342 levels. The total effective rate of the study group was 91.53% after treatment, which was higher than that (74.58%) of the control group ($p<0.05$); the levels of UAER, Scr, BUN and HbA1c, FPG, 2h PG were lowered in the two groups after treatment, and the levels of these indexes were lower in the study group than those in the control group ($p<0.05$); the levels of vWF, ET-1, CD8+, miR-342 were lowered after treatment for the two groups, and the levels of these indexes were lower in the study group than those in the control group; the levels of NO, CD3+, CD4+ and miR-126 were increased after treatment and the levels were higher in the study group than those in the control group ($p<0.05$). The application of hyperbaric oxygen combined with alprostadil in the treatment of elderly DN patients can improve renal function, lower blood glucose, improve vascular endothelial function and immune function, adjust serum miR-126 and miR-342 levels, thereby increasing curative effect.

Keywords: Hyperbaric oxygen, alprostadil, diabetic nephropathy,miR-126; miR-342

INTRODUCTION

Diabetic nephropathy (DN) is a diabetic micro vascular complication. Studies have reported that 20%～40% of diabetic patients will develop DN with a higher incidence in elderly patients (Wang *et al*., 2018). The general manifestation of DN disease in the early stage is microalbuminuria. With the prolonged disease course, renal function can be significantly reduced, leading to renal failure, which is one of the important causes of death in diabetic patients (Nadolnik *et al*., 2018; Umanath *et al*., 2018). Early scientific intervention to delay or reverse kidney damage is the key to treating the disease. The specific pathogenesis of DN is not completely clear, but studies have pointed out that the occurrence and progress of DN may be related to abnormal glucose and lipid metabolism and hemodynamics, oxidative stress injury, and immune system disorders. The treatment of the above pathogenesis may be of positive significance to improve the therapeutic effect.

As a vasodilator, alprostadil can promote vascular dilation, prevent platelet aggregation, inhibit thrombosis and free radical generation, and improve renal blood flow and renal function (Song *et al*., 209; Li ea al., 2019). In recent years, physical therapies such as hyperbaric oxygen have been gradually applied to nephropathy patients. Studies have reported that hyperbaric oxygen can significantly reduce the blood lipid content of patients with primary nephrotic syndrome and improve renal function (Zhang *et al*., 2017). Therefore, it is speculated that the combined application of hyperbaric oxygen and alprostadil in the treatment of elderly DN patients can further improve the therapeutic effect. However, there has been no clinical research reports on this issue. In this study, 118 elderly DN patients were selected for a prospective randomized controlled study, in which the patients solely treated with alprostadil were regarded as controls. The effect of hyperbaric oxygen combined with alprostadil in the treatment of elderly diabetic nephropathy and its effect on patients' serum miR-126 and miR-342 levels were analyzed, which provides a certain basis for clinical exploration of more effective treatments.

MATERIALS AND METHODS

General information

In this work, 118 elderly DN patients treated in our hospital from February 2018 to March 2020 were enrolled as research objects for the prospective randomized controlled study. They were divided into study group (n=59) and control group (n=59) based on random number table. The two groups' general information (age, gender, body weight, diabetes course, DN course, complications, etc.) are balanced and comparable, showing no statistically significant difference ($p>0.05$), as shown in table 1. This study was approved by the ethics committee of our hospital.

Selection criteria

A. Inclusion criteria: Patients meeting the relevant diagnostic criteria of DN in the "Expert Consensus on the Prevention and Treatment of Diabetic Nephropathy (2014

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Edition)", in stage III of DN, with age ≥ 60 years old, with urine albumin excretion rate (UAER) of 20～200 μg/min were included in this study; They had the right to know the treatment plan of this study and signed an informed consent. B. Exclusion criteria: patients severe liver, heart, lung or other organ dysfunction, with primary nephropathy, with diseases in mental system, autoimmune system, blood system, with malignant tumor, acute and chronic infection, with other diabetes complications, as well as patients receiving systemic DN treatment recently, having contraindications to hyperbaric oxygen therapy or being allergic to alprostadil were excluded.

Method

Treatment methods Both groups received conventional treatments such as blood pressure control, blood sugar control, lipid regulation and lifestyle interventions (such as proper exercise, weight control, quitting smoking and drinking, diet adjustment). On this basis, the control group was given alprostadil (Harbin Pharmaceutical Group Holding Co., Ltd., National Medicine Permission Number H20084565): 10μg Alprostadil was dissolved in 100 ml normal saline for intravenous drip, once daily. The study group was given hyperbaric oxygen combined with Alprostadil: A. Hyperbaric oxygen: Medical hyperbaric oxygen chamber (Jiangxi Jiujiang Marine Machinery Factory, GYS-10) was used for treatment. During treatment, the pressure in the air pressurized chamber was increased for 20min to reach 0.25MPa. Constant pressure inhalation of pure oxygen was given for 40min, with 10 min interval for inhalation of chamber air, then decompress for 30 min to normal pressure and exit, 1 time/d, 5 times/week; B. The treatment method and dosage of Alprostadil were the same as the control group. Both groups were treated for 1 month.

Detection method: A: 8 ml cubital venous blood sample was collected from the patients on an empty stomach in the early morning, centrifuged at 3500 r/min for 10 min in a centrifuge to collect the serum and freeze it for testing. An automatic biochemical analyzer (Beckman Coulter, au5800) was used to measure serum creatinine (Scr) and urea nitrogen (BUN) levels, enzyme-linked immunosorbent assay was carried out to detect serum glycosylated hemoglobin (HbA1c) and von Willebrand factor (vWF) levels, glucose oxidase method was used to detect serum fasting blood glucose (FPG) level, radioimmunoassay was used for detection of serum endothelin-1 (ET-1) level, nitrate reductase method was used for detection of serum nitric oxide (NO) level, flow cytometry (Beckman Coulter, FC500) was used for detection of serum CD3+, CD4+, CD8+ levels. Detection kits were all provided by Nanjing Jiancheng Technology Co., Ltd. Real-time fluorescence quantitative polymerase chain reaction method was used for detection of relative expression levels of serum miR-126, miR-342. The kit was purchased from Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.; B: 0.5h after blood sample was taken on empty stomach, glucose tolerance test was performed. 3 mL of blood sample was taken 2 h later, and blood glucose 2h after meal (2h PG) was detected by glucose oxidase method; C: 6 mL of morning urine sample was taken from the patient to detect UAER level by radioimmunoassay. The kit was purchased from Beijing Furui Runze Biotechnology Co., Ltd.

Observation indexes

A: Efficacy. B: Renal function (UAER, Scr, BUN) levels before and after treatment. C: Blood glucose index (HbA1c, FPG, 2h PG) levels before and after treatment. D: Serum vascular endothelial function index (vWF, ET-1, NO) levels before and after treatment. E: Serum immune function index (CD3+, CD4+, CD8+) levels before and after treatment. F: Serum miR-126 and miR-342 levels before and after treatment.

Efficacy evaluation criteria

The treatment is defined very effective if the patient's clinical symptoms disappear, FPG and 2h PG decrease by more than 1/3 or decrease to a normal level, 24h urine protein quantitation and UAER decrease by more than 1/2 or decrease to normal level, renal function returns to norma (Dong *et al*., 2019; Ito *et al*., 2017). The treatment is defined effective if clinical symptoms are relieved, FPG, 2h PG decrease ≤1/3, 24h urine protein quantitation and UAER decrease ≤1/2, renal function basically returns to normal; The treatment is defined invalid if clinical symptoms, FPG, 2h PG, 24h urine protein quantification, and UAER are not significantly improved. The total effective rate = (markedly effective + effective) / total number of cases × 100%.

STATISTICAL ANALYSIS

Research data were input into SPSS 21.0 statistical software for processing, measurement data is expressed as (x ± s), independent sample t test was used for comparison between groups, paired t test was carried out for comparison before and after treatment; count data is expressed in n (%), x^2test was used for comparison between groups. $p<0.05$ indicates statistically significant difference.

RESULTS

Curative effect

After treatment, the total effective rate was higher in the study group than in the control group ($p<0.05$), as shown in table 2.

Renal function indexes

Comparison of UAER, Scr, and BUN levels between the two groups shows no statistically significant difference before treatment ($p>0.05$); UAER, Scr and BUN levels

Table 1: Comparison of general information between the two groups

Data	Study group (n=59)	Control group (n=59)	t / x^2	*P*
Age (years)	60～84(69.42±4.26)	60～86(70.19±4.03)	1.009	0.315
Gender (%)				
Male	36(61.02)	34(57.63)	0.141	0.708
Female	23(38.98)	25(42.37)		
Body weight (kg)	43～87(62.80±7.41)	45～86(62.35±6.83)	0.343	0.732
Course of diabetes (years)	5～21(13.76±2.69)	5～20(13.27±2.58)	1.010	0.315
Course of DN (years)	2～15(9.24±2.07)	3～14(8.84±2.16)	1.027	0.307
Complications (%)				
Hyperlipidemia	14(23.73)	12(20.34)	0.197	0.657
Hypertension	19(32.20)	21(35.59)	0.151	0.697

Table 2: Comparison of efficacy between the two groups n (%)

Group	Number of cases	Invalid	Effective	Markedly effective	Total effective rate
Study group	59	5(8.47)	24(40.68)	30(50.85)	54(91.53)
Control group	59	15(25.42)	23(38.98)	21(35.59)	44(74.58)
X^2					6.020
p					0.014

Table 3: Comparison of renal function indexes between the two groups (x ± s)

Time	Group	Number of cases	UAER(μg/min)	Scr(μmol/L)	BUN(mmol/L)
Before treatment	Study group	59	112.28±14.10	148.61±15.82	13.26±3.18
	Control group	59	115.87±12.93	150.19±16.47	13.54±3.06
	t		1.441	0.531	0.487
	p		0.152	0.596	0.627
After treatment	Study group	59	62.13±6.09a	92.27±10.48a	6.22±1.04a
	Control group	59	87.46±8.35a	109.63±13.24a	9.07±1.48a
	t		18.826	7.897	12.102
	p*		<0.001	<0.001	<0.001

Table 4: Blood glucose index levels of the two groups (x ± s)

Time	Group	Number of cases	HbA1c (%)	FPG (mmol/L)	2h PG(mmol/L)
Before treatment	Study group	59	9.28±0.75	8.39±1.12	10.95±2.04
	Control group	59	9.42±0.84	8.70±1.35	11.28±2.21
	t		0.955	1.358	0.843
	p		0.342	0.177	0.401
After treatment	Study group	59	7.09±0.38[a]	6.75±0.49[a]	8.28±0.56[a]
	Control group	59	8.26±0.45[a]	7.18±0.74[a]	9.67±0.83[a]
	t		15.258	3.722	10.664
	*p**		<0.001	<0.001	<0.001

Table 5: Comparison of serum vascular endothelial function indexes between the two groups (x ± s)

Time	Group	Number of cases	vWF(%)	ET-1(ng/L)	NO(μmol/L)
Before treatment	Study group	59	182.49±29.83	116.57±26.35	47.08±8.92
	Control group	59	185.62±31.79	118.24±28.06	46.24±9.05
	t		0.552	0.333	0.508
	p		0.582	0.740	0.613
After treatment	Study group	59	128.73±18.35[a]	76.24±16.57[a]	98.48±11.86[a]
	Control group	59	152.28±21.46[a]	87.96±20.72[a]	85.75±9.84[a]
	t		6.407	3.393	6.345
	*p**		<0.001	<0.001	<0.001

Note: Compared with this group before treatment, p*<0.05

Table 6: Comparison of serum immune function indexes between the two groups (x ± s, %)

Time	Group	Number of cases	$CD3^+$	$CD4^+$	$CD8^+$
Before treatment	Study group	59	51.16±6.32	33.16±4.29	31.04±3.72
	Control group	59	50.29±6.08	32.82±4.47	32.16±3.53
	t		0.762	0.422	1.678
	p		0.448	0.674	0.096
After treatment	Study group	59	61.14±7.83[a]	40.48±6.45[a]	23.14±2.42[a]
	Control group	59	54.86±6.95[a]	35.36±5.82[a]	27.75±2.60[a]
	t		4.607	4.527	9.969
	*p**		< 0.001	< 0.001	< 0.001

Table 7: Comparison of serum miR-126 and miR-342 levels between the two groups (x ± s)

Time	Group	Number of cases	miR-126	miR-342
Before treatment	Study group	59	0.15±0.09	2.76±0.34
	Control group	59	0.16±0.07	2.82±0.37
	t		0.674	0.917
	p		0.502	0.361
After treatment	Study group	59	0.48±0.13[a]	1.18±0.16[a]
	Control group	59	0.39±0.10[a]	1.57±0.24[a]
	t		4.215	10.386
	*p**		<0.001	<0.001

Note: Compared with this group before treatment, p*<0.05

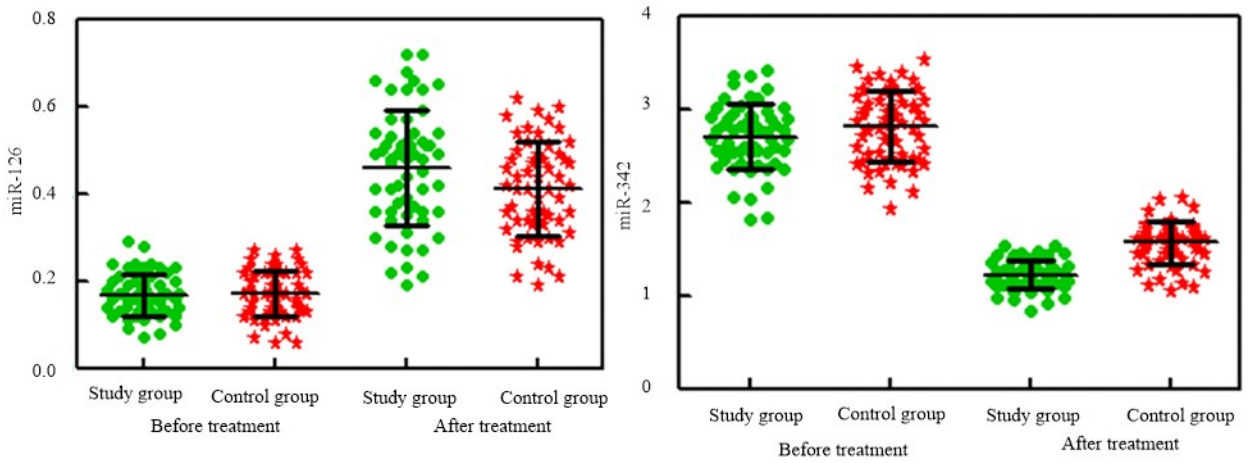

Fig. 1: Comparison of serum miR-126 and miR-342 levels between the two groups

were lowered in the two groups after treatment and the levels of these indexes were lower in the study group than those in the control Group (p<0.05), as shown in table 3.

Blood glucose index

Comparison of HbA1c, FPG, 2h PG levels between the two groups shows no statistically significant difference before treatment (P>0.05); HbA1c, FPG, 2h PG levels were lowered in the two groups after treatment, and the levels were lower in the study group than those in the control group (p<0.05), as shown in table 4.

Serum vascular endothelial function index

Comparison of serum vWF, ET-1, NO levels between the two groups shows no statistically significant difference before treatment (p>0.05); vWF, ET-1 levels were lowered in the two groups after treatment and the levels were lower in the study group than those in the control group; NO level was increased after treatment and the NO level was higher in the study group than in the control group (p<0.05), as shown in table 5.

Serum immune function index

Comparison of serum CD3+, CD4+, CD8+ levels between the two groups shows no statistically significant difference before treatment (p>0.05); serum $CD3+$, $CD4^+$ levels were increased in the two groups after treatment, and the levels were higher in the study group than those in the control group; CD8+ level was decreased after

treatment, and $CD8^+$ level wass lower in the study group than in the control group ($p<0.05$), as shown in table 6

Serum miR-126 and miR-342 levels

Comparison of serum miR-126, miR-342 levels between the two groups shows no statistically significant difference before treatment ($p>0.05$); serum miR-126 level was increased in the two groups after treatment and the study group showed higher level than the control group; miR-342 level was lowered after treatment, and the study group showed lower level than the control group ($p<0.05$), as shown in table 7 and fig. 1.

DISCUSSION

DN has complicated pathogenesis. Studies have pointed out that abnormalities of the endocrine system and immune system are all related to the onset of DN and as the disease progresses, it can even cause renal failure and death (Ding *et al*., 2018; Oreno *et al*., 2018; Lin *et al*., 2019). Alprostadil is a natural prostaglandin substance. (Wang *et al*., 2017) reported that the total effective rate of alprostadil alone in the treatment of elderly DN patients was 59.38%. Alprostadil is a result of the conversion of arachidonic acid, which can dilate the kidney, lung, heart and even the whole body arteries and veins, reduce renal and glomerular vascular resistance, resist platelet aggregation, enhance red blood cell deformability, downregulate blood viscosity, inhibit thrombosis, increase renal blood flow, reduce renal ischemia and hypoxia, improve renal function, and lower urine protein levels. At the same time, studies have reported that alprostadil can also inhibit the body's oxidative stress and inflammation, reduce the degree of microvascular damage and protect vascular endothelial function (Lin *et al*., 2019). This study found that the total effective rate of alprostadil alone in the treatment of elderly DN patients was 74.58%, which was close to the above-mentioned study. It suggests that alprostadil has acceptable therapeutic effect, but the treatment plan still needs further improvement. Recently, hyperbaric oxygen has become an important adjuvant treatment option in the treatment of kidney disease patients, Lin Jinsong *et al*. reported that the application of hyperbaric oxygen in adjuvant treatment of patients with chronic kidney disease can significantly improve the patient's blood rheology and help improve renal function (Shen *et al*., 2018). Shen Jiaojiao *et al*. confirmed through experimental studies that hyperbaric oxygen assistance can significantly improve the drug treatment effect on mice with IgA nephropathy and improve renal function (Chen *et al*., 2019). This study also found through prospective randomized controlled study that the total effective rate of hyperbaric oxygen combined with alprostadil in the treatment of elderly DN patients was up to 91.53%, and the patients showed more significant renal function improvement and blood glucose level reduction after treatment.

The possible mechanism of hyperbaric oxygen therapy for DN is that hyperbaric oxygen can reduce insulin hormone content, regulate acid-base imbalance, promote S-peptide secretion, improve tissue sensitivity to insulin, and help reduce blood sugar levels; moreover, it can also relieve renal ischemia, increase glomerular filtration, promote urine formation, increase creatinine excretion rate, lower BUN level, and improve renal function. At the same time, it can increase blood oxygen content, increase oxygen partial pressure, enlarge effective oxygen diffusion range, increase capillary end oxygen partial pressure, correct tissue hypoxia, reduce blood viscosity, resist platelet aggregation, promote the dissolution and absorption of micro thrombosis and then effectively improve the body's microcirculation, reduce urine protein excretion, and improve the therapeutic effect; finally, it canalso improve the immune function and vascular endothelial function (Liu *et al*., 2018).

CD3+, CD4+ and CD8+ are all important indicators of cellular immune function. Where, CD3+ is mature T lymphocyte, whose expression is positively correlated with cellular immune function state; CD4+ is helper T cell that can enhance the body’s immune function; CD8+ is inhibitory T cell that can reduce the body's immune function (Keating *et al*., 2018). This study found that after the application of hyperbaric oxygen combined with alprostadil, patients' CD3+ and CD4+ levels increased, and CD8+ levels decreased more significantly, indicating that hyperbaric oxygen combined with alprostadil can synergistically improve patients’ immune function. Hyperbaric oxygen therapy can regulate the immune system function of the body, inhibit the generation of immunoglobulin and immune complex, improve the ability of phagocytosis and digestion of immune complex of macrophages, inhibit the generation of local immune response, and promote the recovery of immune function (Zeng *et al*., 2019). vWF is one glycoprotein which can be released into the blood when vascular endothelial cells are damaged. Its expression level is positively correlated with the degree of vascular endothelial injury. ET-1 is a vasoactive peptide, whose increased expression can cause renal vasoconstriction, reduce renal blood flow, increase glomerular filtration rate, and increase the expression of urinary protein. Insufficient NO secretion can also lead to increased vasoconstriction, glomerular blood flow disorder, and worsen the condition of DN (Tao *et al*., 2017). This study showed that after treatment with hyperbaric oxygen combined with alprostadil, vWF and ET-1 levels decreased and NO level increased more significantly. It indicates that hyperbaric oxygen combined with alprostadil can synergistically regulate the patient's vascular endothelial function. The possible reason is that hyperbaric oxygen can increase oxygen diffusion capacity in tissue capillaries, prevent vascular endothelial injury, increase the level of vascular endothelial cell growth factor and improve vascular

endothelial function. Xu Tianyang *et al*. found that hyperbaric oxygen can reduce patients' ET-1 level, increase NO level, and protect vascular endothelial function (Quan *et al*., 2018). Recent studies have found that miRNA has been proven to play an important role in biological processes such as cell metabolism, proliferation, differentiation and apoptosis (Xu *et al*., 2019). Both miR-126 and miR-342 are important miRNAs. Where, miR-126 plays an important role in angiogenesis, whose decreased expression has close relation with DN and diabetic microvascular damage. miR-342 closely related to atherosclerosis can regulate expression of several inflammatory signaling pathways and cytokines, whose high expression is related to the occurrence and progression of DN (Li *et al*., 2019; Zhong *et al*., 2018). In this study, miR-126 level increased and miR-342 level decreased more significantly after treatment with hyperbaric oxygen combined with alprostadil. It suggests that application of hyperbaric oxygen combined with alprostadil can effectively regulate serum miR-126 and miR-342 levels, but the specific mechanism of action still needs further analysis in the future. In addition, as an antioxidant, alprostadil may induce pro-oxidation in the case of large dose application, so close attention should be paid to the injection dose in the application process to avoid negative effects caused by excessive application. The possibility of hyperbolic oxygen therapy and the effect of different doses of alprostadil remain to be discussed.

CONCLUSION

To conclude, the application of hyperbaric oxygen combined with alprostadil in the treatment of elderly DN patients can improve renal function, lower blood glucose, improve vascular endothelial function and immune function, regulate serum miR-126 and miR-342 levels, thereby improving curative effect.

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