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A Randomized Controlled Trial to Investigate the Efficacy of Folic Acid and Vitamin B in Reducing Serum Homocysteine and Improving Left Ventricular Hypertrophy in Patients with End-Stage Renal Disease

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Abstract

Objectives: To investigate the efficacy of oral folic acid, vitamin B12 and vitamin B6 in reducing serum homocysteine and improving left ventricular hypertrophy in End-Stage Renal Disease (ESRD) patients.

Methods: A total of 105 patients with ESRD were enrolled. The experimental group (n = 50) received folic acid, vitamin B12 and vitamin B6 orally, while the control group (n = 53) did not take the above drugs.Serum homocysteine was examined at baseline and one year later, and the left ventricular hypertrophy index was calculated by perfect echocardiography. The differences of homocysteine and left ventricular hypertrophy index between the two groups were compared.

Findings Conclusion: Hcy: 18.62±8.12μmol/L in the experimental group was significantly lower than 25.46±16.13μmol/L in the control group (P=0.008). LVEDD: The experimental group 46.36±5.73mm was significantly lower than the control group 49.68±7.56mm (P=0.014); LVMI: 119.87±35.37g/m2 in the experimental group and 141.82±46.91g/m2 in the control group decreased significantly (P=0.008).

Conclusion: Oral administration of folic acid, vitamin B12 and vitamin B6 can reduce serum homocysteine and left ventricular hypertrophy index in ESRD patients.

Keywords: End-stage renal disease; Folic acid; Homocysteine; Left ventricular hypertrophy; Vitamin b

Abbreviations: ESRD: End-Stage Renal Disease; CKD: Chronic Kidney Disease; CVD: Cardiovascular Disease; Hcy: Homocysteine; hHcy: Hyperhomocysteinemia; IVST; Interventricular Septum Thickness; LVEDD: Left Ventricular End Diastolic Dimension; LVEF: Left Ventricular Ejection Fraction; LVM: Left Ventricular Mass; LVMI; Left Ventricular Mass Index; LVPWT: Left Ventricular Posterior Wall Thickness; MHD: Maintenance Hemodialysis; PD: Peritoneal Dialysis.

Introduction

The global incidence of Chronic Kidney Disease (CKD) is between 8% and 16%, and it has become a global public health problem [1], Its incidence is increasing by about 6% a year [2], As the disease progresses, CKD progresses to End-Stage Renal Disease (ESRD), requiring renal replacement therapy to maintain life. Renal replacement therapy includes Hemodialysis (MHD), Peritoneal Dialysis (PD), and kidney transplantation.The proportion of CKD patients with Cardiovascular Disease (CVD) was about 40.6% [3], About 52% of ESRD patients had CVD [4], About half of the deaths of ESRD patients are attributed to CVD [5].

The most common changes in CVD are changes in left ventricular structure and function. Left Ventricular Hypertrophy (LVH) is an independent predictor of cardiovascular death [6], Echocardiographic diagnosis of LVH, Left Ventricular Mass Index (LVMI) can reflect the degree of left ventricular hypertrophy.The prevalence of LVH in patients with CKD is higher than that in the general population [7], When ESRD patients enter dialysis, the in-

cidence of LVH can be more than 70% [8].

CKD patients are often accompanied by increased hcy due to decreased homocysteine clearance ability of the kidneys. The incidence of h-hcy in ESRD patients is about 85% [9]. Folic acid combined with vitamin B6 and vitamin B12 is commonly used in the treatment of hyperhomocysteinemia (h-hcy). The mechanism is to accelerate the metabolism of hcy [10]. Less attention has been paid to whether reducing the level of hcy in patients with ESRD can reverse LVH. The purpose of this study was to investigate whether folic acid, vitamin B12 and vitamin B6 can reduce the level of hcy and improve the status of LVH in patients with ESRD through randomized controlled trials.

Patients and methods

- Participants: patients with MHD and PD in Sun Yat-Sen University, Yuedong Hospital from January 2019 to June 2020 were followed up for one year.
- Inclusion criteria: (1) patients with MHD or PD; (2) without significant heart failure [New York Heart Association III or IV]).
- Exclusion criteria: (1) infection occurred within 1 month before selection; (2) acute cardiovascular events occurred within 1 month before selection; (3) use of hormones or immunosuppressants; (4) patients with malignant tumor, mental illness or pregnancy.
- The subjects were divided into two groups: before the beginning of the trial, all patients were eluted with drugs for 6 weeks, and then the patients were randomly divided into two groups. The experimental group was given oral folic acid tablets 15mg/d, vitamin B6 tablets 30mg/d, vitamin B12 tablets 1.5mg/day, while the control group did not take the above-mentioned drugs orally.

Baseline Data Collection and Biochemical Evaluation

The baseline variables included demographic indicators (age, sex, height, weight). Laboratory examination: serum homocysteine was tested and blood was drawn from hemodialysis patients before dialysis began. (6) Echocardiography: The Left Ventricular Ejection Fraction (LVEF), Left Ventricular Posterior Wall Thickness (LVPWT), Interventricular Septum Thickness (IVST) and left ventricular end-diastolic diameter (LVEDD) were measured and recorded by color Doppler echocardiography at baseline and one year later. Calculation of left Ventricular Mass Index (LVMI) according to Devereux Formula [11], LVMI=Left Ventricular Mass (LVM)/ Body Surface Area (BSA), LVM=1.04×[LVEd+IVST+LVPWT) 3-LVDd3]+13.6, BSA(m^2)=0.0061×Height (cm)+0.0128×Weight (kg)-0.1529. LVH diagnostic criteria: male LVMI>125g/m^2, female LVMI>120g/m^2.

Statistical analyses

The data were analyzed by SPSS22.0 software, and the continuous variables were expressed by mean ±standard deviation. The measurement data in accordance with normal distribution were expressed as x ±s, t-test was used, counting data was expressed as percentage, and χ^2 test was used for comparison between groups.

Results

Baseline data analysis

103 cases in groups, 50 cases of the experiment group,Age 63.24±11.09 years old，33 males (66%), 33 MHD (66%), HCY: 30.26±17.04, LVMI: 123.61±28.48.In the control group, there were 53 patients (age 61.34±12.12 years old), 34 males (64.2%), 36 MHD patients (67.92%), HCY: 27.79±15.59, LVMI: 137.01±45.97,hcy：27.79±15.59，LVMI：137.01±45.97 。There was no significant difference in the observation items between the two groups at baseline (P > 0.05) (Table 1).

Variable	Experimental group (n=50)	Control group (n=53)	t/χ^2/Z	P
Age(Years)	63.24±11.09	61.34±12.12	0.829	0.409
Gender, (% male)	33 (66%)	34 (64.2%)	0.039[a]	0.844
Renal replacement (% MHD)	34 (68%)	36 (67.92%)	0.000[a]	0.993
Height(cm)	161.05±9.08	160.12±12.79	0.422	0.674
Weight (kg)	59.78±9.75	60.58±11.29	-0.384	0.701
HCY(μmol/L)	30.26±17.04	27.79±15.29	0.44	0.44
LVEF(%)	64.3%±7.52%	61.47%±11.43%	0.004	0.144
LVPWT (mm)	11.41±1.96	11.55±1.68	-0.403	0.688

IVST(mm)	11.74±1.52	11.83±1.83	-0.271	0.787
LVED(mm)	45.98±4.78	47.96±6.71	-1.719	0.089
LVMI(mm)	123.61±28.48	137.01±45.97	-1.766	0.08

Table 1: Baseline data of subjects.

Analysis of follow-up results

There were no significant differences in LVEF, LVPWT and IVST between the two groups (P > 0.05). Hcy: the experimental group was 18.62±8.12μmol/L, compared with the control group: 25.46±16.13μmol/L significantly decreased (P=0.008). LVEDD:The experimental group 46.36±5.73mm was significantly lower than the control group: 49.68±7.56mm (P=0.014); LVMI: the experimental group was 119.87±35.37g/m2, significantly lower than the control group: 141.82±46.91g/m2 (P=0.008) (Table 2).

Variable	Experimental group (n=50)	Control group (n=53)	$t/\chi^2/Z$	P
HCY(μmol/L)	18.62±8.12	25.46±16.13	-2.738	0.008
LVEF(%)	62.7%±10.76%	59.62%±12.52%	1.335	0.185
LVPWT (mm)	11.04±1.61	11.42±1.71	-1.132	0.26
IVST(mm)	11.24±1.59	11.68±2.03	-1.22	0.225
LVED(mm)	46.36±5.73	49.68±7.56	-2.5	0.014
LVMI(mm)	119.87±35.37	141.82±46.91	-2.691	0.008

Table 2: Comparison of the two groups after intervention.

Limitations

There are many risk factors for CVD in patients with ESRD, including age, hypertension, anemia, high serum triglyceride, high serum uric acid, high serum phosphorus, elevated C-reactive protein and so on.In this study, we only analyzed the effects of folic acid, vitamin B12 and vitamin B6 on hcy and LVMI. Do not rule out other factors and interfere with the conclusion at the same time.

Discussion

Hcy is the intermediate product of methionine metabolism in the body. The daily production of methionine is 15-20 umol/L, and it is mainly metabolized through the kidney in the body.CKD patients are often associated with elevated hcy. When nephropathy progresses to ESRD, the incidence of hyperhomocysteinemia can reach 85%. The reasons for HCY increase are (1) the glomerular filtration rate decreased, because the kidney is the main organ for clearing HCY, HCY accumulated in the body due to the decrease of clearance, (2) the activity of metabolic enzymes decreased or lacked: CBS and MTHFR were widely distributed all over the body, and the activity was the highest in the kidney, and CKD could lead to the deficiency of these two enzymes. A number of studies have shown that oral folic acid tablets, vitamin B12 and vitamin B6 tablets are the first choice for reducing homocysteine [12-14], Hcy promotes left ventricular dilatation [15]. Hcy induces dysfunction of endothelial cells through toxicity, which may be the pathogenic basis of various diseases [16], so as to promote vascular remodeling and accelerate the development of CVD [17]. And the appearance of LVH is the symbol of CVD [18], and can lead to an increase in CVD risk [19].

This study confirmed that oral folic acid, vitamin B12 and vitamin B6 can significantly reduce the level of hcy, which is the same as that of other studies.This study also found that one year after oral administration of folic acid, vitamin B12 and vitamin B6, echocardiography showed that LVEDD and LVMI were significantly lower than those one year ago, indicating that reducing hcy, can reduce the level of LVMI, alleviate the degree of LVH, and then have a protective effect on CVD.

Conclusion

Oral administration of folic acid, vitamin B12 and vitamin B6 can reduce serum homocysteine and left ventricular hypertrophy index in patients with ESRD.

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