Comparison of Oral Folic Acid and Folinic Acid on Blood Homocysteine Level of Patients on Hemodialysis

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Introduction. Hyperhomocysteinemia is common in patients with chronic kidney disease. There is a direct relationship between cardiovascular mortality and increase of blood homocysteine. Folic acid is used as common treatment in such patients. Folinic acid, a shortened form of folic acid, is not affected by inhibitors of dihydrofolate reductase enzyme such as methoterxate. This study was performed to evaluate the effect of oral folinic acid on the blood homocysteine level of hemodialysis patients, in comparison with folic acid.

Materials and Methods. This clinical trial was performed on 60 hemodialysis patients. The participants were divided into 2 groups to receive either 15 mg of oral folic acid or 15 mg of oral folinic acid, daily. Blood homocysteine levels were measured before dialysis and after the study period.

Results. Folic acid and folinic acid decreased the blood homocysteine levels by 33.0% and 28.7%, respectively ($P < .001$). However, only 3 patients (6.5%) enjoyed a normalized homocysteine level.

Conclusions. Our study showed that both folic and folinic acid decreased the blood homocysteine level and no meaningful difference was observed between them; therefore, we suggest they can be used interchangeably.

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INTRODUCTION

Elevated blood homocysteine is seen in 85% to 100% of patients with chronic kidney disease.[1-3] Hyperhomocysteinemia increases cardiovascular risk, one of the most important causes of death in patients with end-stage renal disease (ESRD).[4-6] It is also considered as an independent risk factors of poor outcomes in ESRD.[7-9] In comparison with general population, myocardial infarction has been reported to be 4- to 20-fold more common in ESRD patients,[4,10] and a 25% decrease of plasma homocysteine can reduce the risk of cardiac ischemic disease by 11% and the risk of myocardial infarction by 20%.[3]

Homocysteine is an intermediary amino acid in the methionine-to-cysteine conversion pathway. This amino acid is endogenous and is not taken from daily diet. In fact, homocysteine is considered as an intermediary metabolite in methionine metabolism.[1] The fasting concentration of plasma homocysteine is 5 µmol/L to 15 µmol/L in healthy people.[10]

Folic acid ($C_{19}H_{19}N_7O_6$) is a known factor in transporting active monocarbon unit of methyl in the conversion of homocysteine to methionine. Folinic acid (5-formyl derivative of 5-tetrahydrofolate) is the shortened form of folic acid, which is easily converted to decreased forms of folic acid

derivatives such as tetrahydrofolate, and its function as a vitamin equals to folic acid. This vitamin does not need dihydrofolate reductase. Thus, it is not affected by inhibitors of dihydrofolate reductase enzyme such as methoterxate. The antioxidation effect of folinic acid resembles that of vitamin E, which inhibits lipid peroxidation. Such an effect decreases the risk of atherosclerosis in hemodialysis patients.[9] Due to the fact that a lower homocysteine level is associated with a lower cardiovascular risk in patients with chronic kidney failure,[6,10,11] among different ways of reducing homocysteine level, administration of folic acid[1,12-14] and folinic acid[15-18] is highly recommended.

Although intravenous form of folinic acid proves to further decrease plasma homocysteine level in comparison with the oral form, some studies have shown that the effect of short-period consumption of oral and intravenous forms is similar on blood homocysteine level of hemodialysis patients.[19] Little research has been done to show the efficacy of oral folinic acid on blood homocysteine level of hemodialysis patients. This study is conducted to investigate this effect of oral folinic acid in these patients and to compare it with the current medication, which is folic acid.

MATERIALS AND METHODS

Among patients of the dialysis center of Akhavan Hospital in Kashan (a city in the center of Iran), 60 patients on hemodialysis for more than 6 months, using low-flux filter were selected to participate in this study. The protocol of the study was approved by the local Committee on Ethics in Medical Studies. All patients who agreed to undergo the treatment process were nonsmoker, aged 15 years and over, and without severe cerebrovascular disease or cancer. All participants, previously taking 5 mg/d of folic acid, 100 µg of vitamin B12, and 100 µg of vitamin B-complex in each session of dialysis, were divided into 2 groups of 30 in order to receive either folic acid or folinic acid. In uremic patients, high doses of oral folic acid are required to decrease plasma total homocysteine concentrations. The reasons are unclear, but uremic patients seem to have an insufficient intestinal absorption of folic acid and/or slow metabolism to the active forms of folate.[4] Therefore, we administered high doses of folic acid (15 mg/d) and folinic acid (15 mg/d) for 8 weeks. The patients also continued to receive their routine intravenous vitamin B preparation throughout the study.

To determine the blood homocysteine levels before dialysis, fasting blood samples were collected at the start and end of the study. The blood homocysteine level was measured before and after the medication using enzyme immunosorbent assay method (Axis Shield, Dundee, UK). The results were also confirmed in a different laboratory. We defined a high homocysteine level to be greater than 10 µmol/L.

All the data consisting of patients' demographic information, type of medication, and laboratory tests before and after the study period were collected in one form. Statistical analyses were done using the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA). To compare blood homocysteine levels and the decrease of homocysteine level before and after medication, the Mann-Whitney test and the Wilcoxon sign rank test were used, respectively. In all statistical tests, the differences were considered to be significant if *P* value was less than .05.

RESULTS

Twelve patients were excluded from the study owing to death, kidney transplantation, and wrong use of medication. Therefore, 48 patients (28 women and 20 men) underwent the study, of whom 22 took oral folic acid and 26 took oral folinic acid tablets. The mean age was 56.1 ± 14.2 years in the folic acid group and 58.2 ± 14.6 years in the folinic acid group. Before the study period, blood homocysteine level of 1 patient in the folic acid group was within normal range (<10 µmol/L) and all other patients in the two groups had blood homocysteine levels higher than normal. Folic acid and folinic acid decreased blood homocysteine

Blood Homocysteine Levels Before and After Treatment of Patients on Hemodialysis With Folic Acid and Folinic Acid

	Study Group		
Homocysteine	Folic Acid	Folinic Acid	*P*
Baseline, µmol /L	21.67 ± 6.66 (8.9 to 32.1)	22.49 ± 5.59 (12.4 to 35.1)	< .001
After 8 weeks, µmol /L	14.74 ± 4.73 (13.4 to 22.6)	16.05 ± 4.75 (6.7 to 27.7)	< .001

levels of hemodialysis patients by 33.0% and 28.7%, respectively (Table). Blood homocysteine levels were not significantly different between the 2 groups neither before nor after the study period. Three patients (6.5%) had a normal homocysteine level at the end of the study.

DISCUSSION

In our study, folic and folinic acid decreased blood homocysteine level of hemodialysis patients by 33% and 28.7%, respectively ($P < .001$). No meaningful differences were observed between the two study group in homocysteine levels of the baseline and outcome. Other studies have conducted on folic acid and folinic acid could not find any significant difference between the two medications in lowering total homocysteine of hemodialysis patients.[15,20-25] Therefore, folinic acid could be an appropriate substitute of folic acid, which has some specific limitations such as the need for dihydrofolate reductase.

However, there are some disagreements among investigations showing that high doses of folic acid or folinic acid cannot significantly decrease the plasma total homocysteine of homodialysis patients. For example, Gonin and colleagues showed that high-dose oral folic acid and intravenous folinic acid are ineffective at lowering total homocysteine in patients on hemodialysis when given together with folinic acid, serine, or B vitamins in addition to routine folic acid and B vitamin supplements.[26] Anderson and associates demonstrated that a 12-week course of therapy with folinic acid (50 mg, intravenous, once weekly) in 34 ESRD patients failed to lower homocysteine levels compared with placebo.[27] Probable reasons of inadequate efficacy of folic acid and folinic acid on reduction of blood homocysteine level of hemodialysis patients in some studies are as follows: the first probable reason is that therapeutic dosages of folic and folinic acid had not been adequate to meet the need for them.[28] Most studies, like ours, used high doses of folic acid or folinic acid. One reason is that water soluble vitamins can be excreted through dialysis membranes and high doses of them can compensate some of their wasting.[29,30] In the study of Ossareh and cworkers, increasing folic acid dose from 10 mg/d to 15 mg/d made a significant decrease in homocysteine levels.[30]

Short course of folate therapy is another reason of suboptimal effect on homocysteine. It seems that longer course of treatment with folates leads to more decreasing level of homocysteine.[30] In our study, 2-month treatment caused significant difference in blood homocysteine level of homodialysis patients. Furthermore, we had started a low dose of folate therapy (5 mg/d) at least 6 months before the study period, and this time would be enough for maximal effect of folic acid.[30]

Simultaneous consumption of some drugs such as lipid-lowering and antihypertensive drugs can increase serum levels of homocysteine.[31] All of our patients were administered with such drugs too, but it is probable that high doses of folates and co-administration to B vitamins in our study have compensated such drugs' effects. Inadequate prescription and/or no supervision on regular intake of B vitamins and folates may potentially lead to unfavorable homocysteine levels.[30,32,33] Azadibaksh and colleagues achieved the least homocysteine level with a high dose of folic acid in combination with vitamin B12.[34] Although intravenous form of folinic acid seems to decrease more plasma homocysteine level in comparison with the oral form, some studies have shown that the effect of short-period consumption of oral and intravenous forms is similar in blood homocysteine level of hemodialysis patients.[19]

CONCLUSIONS

In our study, folic acid and folinic acid could normalize the blood homocysteine level of only 3 patients (6.5%). This is a property of these vitamins that always are able to lower, but not able to normalize the blood homocysteine level of hemodialysis patients.[23,25,30] Regarding our study, both oral folic and folinic acid can decrease blood homocysteine level of hemodialysis patients. We suggest the use of folinic acid in order to prevent folic acid limitations.

CONFLICT OF INTEREST

None declared.

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