Effect of Short-Term Folate and Vitamin B Supplementation on Blood Homocysteine Level and Carotid Artery Wall Thickness in Chronic Hemodialysis Patients

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Objective: *Hyperhomocysteinemia is an independent risk factor for atherosclerotic vascular disease in chronic hemodialysis patients. This stratified randomized controlled trial was designed to measure the effect of high dose oral vitamin B6, vitamin B12, and folic acid on homocysteine levels, and to evaluate the effect on atherosclerosis as measured by Intima-Media Thickness (IMT) of carotid arteries.*
Material and Method: *Fifty-four chronic hemodialysis patients with hyperhomocysteinemia were randomized to receive oral 15 mg folic acid, 50 mg vitamin B6, and 1 mg vitamin B12 daily (treatment group) or oral 5 mg folic acid alone (control group) for 6 months. Homocysteine level and IMT were measured in both groups.*
Results: *At 6 months, homocysteine levels in the treatment group were significantly reduced from 27.94 8.54 to 22.71 3.68 mmol/l (p = 0.009) and were not significantly increased from 26.81 7.10 to 30.82 8.76 mmol/l in control group (p = 0.08). Mean difference between both groups was statistically significant (p = 0.002). There was no significant difference of IMT of carotid arteries, however, a tendency that the treatment group would have less thickness was observed (0.69 0.29 mm and 0.62 0.16 mm, p = 0.99).*
Conclusion: *Treatment of hyperhomocysteinemia in chronic hemodialysis patients with daily oral 15 mg folic acid, 50 mg vitamin B6, and 1 mg vitamin B12 for 6 months decreases homocysteine levels and tends to reduce IMT of carotid arteries. A long term study for the prevention of atherosclerosis is warranted.*

Keywords: *Atherosclerosis, Carotid artery wall thickness, Folate, Hemodialysis, Homocysteinemia, Vitamin B6, Vitamin B12*

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Hyperhomocysteinemia is an independent risk factor for atherosclerosis in chronic hemodialysis patients[1]. They have hyperhomocysteinemia 2-4 fold higher than normal population[2]. A randomized trial found a significant reduction of post-methionine total homocysteine with vitamin B6 treatment in uremic patients[3]. As the presence of a suboptimal vitamin B12 status in end stage renal disease patients, administration of vitamin B12 is recommended. Both vitamin B6 and B12 are the important cofactors in homocysteine metabolism[4]. Supplementation with folic acid, vitamin B6, B12 can reduce total homocysteine concentrations by 33% in the general population[5].

Folic acid and vitamin B6 treatment resulted

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in the lowering of plasma homocysteine and amelioration of endothelial damage[6]. Combinations of folic acid and vitamin B6 and B12 can most efficiently lower plasma Hcy concentration, irrespective of the causes of hyperhomocysteinemia both in patients and in healthy individuals[7,8]. Besides, there was evidence of reduction of carotid atheromatous plagues size with folic acid, vitamin B6 and B12[7].

Ultrasonographically measured carotid Intimal Media Thickness (IMT) is a marker for early atherosclerotic changes[9], coronary heart disease and cerebral ischemic events[10,11]. The method is non-invasive with sufficient accuracy and reproducibility to be reliable for short time longitudinal studies[10]. IMT correlates positively with plasma Hcy concentration in the general population[12,13]. IMT has already been used as a suitable end point for anti-atherosclerotic intervention trials directed towards different risk factors, e.g. hypercholesterolemia[14]and hypertension[15].

Whether aggressive treatment of hyperhomocysteinemia can regress and slow progression of atherosclerosis is not established. The authors thus conducted the present study to evaluate the effect of supraphysiologic dose of folic acid combination with vitamin B6 and vitamin B12 on total homocysteine levels and carotid wall thickness in chronic hemodialysis patients.

Material and Method

Study population

Fifty-four patients with homocysteine levels > 10 mmol/l were enrolled in the present study. Exclusion criteria include age > 75 or < 20 years old, alcohol drinking, smoking, malnutrition (albumin < 3 g/dl), current use of metrotrexate, trimetroprim, phenytoin, carbamazepine, theophylline, underlying disease such as malignancy, infection, systemic disease (autoimmune disease, SLE, RA, hypothyroid). All participants had mean fasting total plasma homocysteine levels 27.8 mmol/l when determined as part of the initial cross-sectional, analytic study[16]. The study protocol was approved by the Ethical Committee of Siriraj hospital and all participants gave their written informed consent prior to participation.

Study protocol

The patients with hyperhomocysteinemia were randomized to receive daily oral 15 mg of folic acid, 50 mg of vitamin B6 and 1 mg of vitamin B12 (treatment group) or daily oral 5 mg folic acid alone (control group) for six months (July 2003 - January 2004). Clinical biochemistries, total homocysteine levels and IMT of carotid arteries were measured in both groups at baseline and at sixth month therapy.

Laboratory and clinical data

Blood samples were obtained fasting at least 12 hours, pre-hemodialysis at the baseline and after six months of treatment and control group. They were immediately cooled at 4 C and centrifuged within 30 minutes at 2000 g at 4 C. The separated plasma was snap-frozen and stored at -70 C. Measurement was done of plasma homocysteine (fluorescence polarization immunoassay method, ABBOT Laboratories - The IMx Homocysteine), erythrocyte B6 (erythrocytes glutamate oxaloacetate transaminase activity and activity after stimulation with Pyridoxal-5-Phosphate (P-5-P), described by Hoffman CA Roche), plasma B12 (electrochemiluminescence immunoassay "ECLIA", Boehringer Mannheim - Elecsys vitamin B12 Immunoassay), plasmafolate (electrochemiluminescence immunoassay "ECLIA", Boehringer Mannheim - Elecsys folate Immunoassay). Routine monthly clinical chemistry profiles were performed using standard methods.

Carotid ultrasound measurement

B-mode ultrasonography of carotid artery was performed with high-resolution, real time scanner equipped with a Toshiba, power vision 6000, 7.5 MHz imaging transducer. One trained radiologist, who was blinded with regard to the subject's clinical data, examined the patients who were in supine position by scanning each side of the neck at the common carotid artery, carotid bulb, and measured IMT of both Common Carotid Arteries (CCA). Each subject had IMT measured on the far wall of the distal CCA, because, this site has been demonstrated to yield greater precision and reproducibility[17]. The IMT image, obtained from the plaque-free area of the CCA and at least 1 cm and 2 cm away from the origin of the bulb, and measured by longitudinal view, consisted of two parallel echogenic lumen intima and media adventitia interfaces.

Statistical analysis

All case record files were evaluated and analyzed using the SPSS program for window packages. The data was presented as mean $\pm$ SD or percent. Changes of total homocysteine levels and IMT between treatment group and control group were compared by using independent t-test. Changes of the outcome in the same individual were compared using paired *t*-test. A p-value of less than 0.05 was considered significant.

Results

Fifty-four patients were randomized to receive oral daily folic acid, vitamin B6 and vitamin B12 as treatment group (n = 27) and oral daily folic acid alone as control group (n = 27). In the treatment group, three died (2 septicemia, 1 acute myocardial infarction), two under-went kidney transplantation and one developed pulmonary tuberculosis, whereas in the control group, three died (1 septicemia, 2 acute myocardial infarction) and one underwent kidney transplantation. Hence, there were 21 patients in the treatment group and 23 patients in the control group for analysis. Baseline characteristics of both groups were not statistically significantly different (Table 1). No patient had plasma folate, vitamin B6 or vitamin B12 deficiency at baseline, as defined by normal laboratory values (Table 1).

At 6 months, total homocysteine levels in the treatment group were reduced from 27.94 $\pm$ 8.54 to 22.71 $\pm$ 3.68 mmol/l and showed statistically significant difference (p = 0.009) as shown in Fig. 1 and were increased from 26.81 $\pm$ 7.10 to 30.82 $\pm$ 8.67 mmol/l in control group but without statistically significant difference (p = 0.08) as shown in Fig. 2.

The mean difference between both groups was statistically significant (p = 0.002) as shown in Table 2. A tendency that treatment group would have lower thickness was observed (0.69 $\pm$ 0.29 mm and 0.62 $\pm$ 0.16 mm, p = 0.99) as shown in Fig. 3 and 4. There was no significant difference of IMT of carotid arteries as shown in Table 2. The treatment group was not associated with any adverse effect symptoms.

Discussion

The present study showed that chronic hemodialysis patients had hyperhomocysteinemia similar to previous studies. Bostom et al found that 83% of chronic hemodialysis patients had hyperhomocysteinemia (fasting level > 13.9 μmol/l)[1]. Data also demonstrated a reduction of plasma homocysteine levels clearance in the uremic state[18]. However, if this resulted from reduced homocysteine renal clearance, by the presence of uremic toxins or a combination of these factors remained to be clarified[19]. It was noteworthy that an alteration of the remethylation pathway, but not of the transsulfuration pathway, had been demonstrated in these patients[19].

The previous study revealed that a subclinical deficiency of folic acid and vitamin B12, two cofactors needed in the remethylation, particularly, folate, played an essential role via its action metabolite, 5-Methyl Tetra Hydro Folate (MTHF)[19]. However, the presented patients had normal or higher levels of folate and vitamin B6, B12. After 6 months of therapy, the treatment group had shown that total homocysteine levels reduced by 11.6%. This compare favorably with another study that showed a 20-30% reduction in total homocysteine levels[5]. The difference in the lowering effect was probably due to relative resistance to folate action presented in uremia[19] and the multiple abnormalities of the remethylation pathway that were not related to folate such as relative resistance to vitamin B6 and/or B12[19].

Multiple dose regimens were proposed in the literature[20-24]. It is accepted that supraphysiologic

Table 1. Baseline characteristics of both groups (mean $\pm$ SD) (n = 54)

	Control (27)	Treatment (27)	p-value
Age (years)	55.17 $\pm$ 13.86	55.86 $\pm$ 13.44	0.86
Sex (%male)	47.8%	42%	0.98
Duration of HD (months)	59 $\pm$ 46.4	60 $\pm$ 48.3	0.21
Weekly Kt/v	2.04 $\pm$ 0.54	2.05 $\pm$ 0.48	0.93
Hcy (mmol/l)	27.5 $\pm$ 7.73	27.9 $\pm$ 8.55	0.86
Mean IMT (mm)	0.59 $\pm$ 0.12	0.68 $\pm$ 0.29	0.13
Ca x P	58.21 $\pm$ 23.8	56.51 $\pm$ 17.58	0.79
Cholesterol (mg/dl)	174.7 $\pm$ 45.1	185.4 $\pm$ 31.5	0.37
Triglyceride (mg/dl)	59 $\pm$ 46.4	116.2 $\pm$ 43.2	0.18
HDL-cholesterol (mg/dl)	48.1 $\pm$ 16.9	46.29 $\pm$ 11.9	0.68
Systolic BP (mmHg)	149.2 $\pm$ 17.55	148.6 $\pm$ 21.97	0.93
Diastolic BP (mmHg)	80.65 $\pm$ 9.23	81.24 $\pm$ 8.67	0.83
Folate (ng/ml)	58.21 $\pm$ 23.8	56.51 $\pm$ 17.58	0.79*
Vitamin B6(activation coefficient)	0.59 $\pm$ 0.46	1.16 $\pm$ 0.43	0.18
Vitamin B12 (ng/ml)	48.1 $\pm$ 16.9	46.29 $\pm$ 11.9	0.68*

*Normalized data distribution by $\log_e$ (ln)

Table 2. Effect of vitamin B supplement on the levels (mean ± SD) of homocysteine, folate, B6, B12, BP and IMT (n = 54)

	Control (27)			Treatment (27)			p-value	
	0 mos	6 mos	p-value	0 mos	6 mos	p-value	0 mos	6 mos
Homocysteine (mmol/l)	26.8±7.73	30.8±7.8	0.08	27.9±8.55	22.7±6.5	0.009	0.86	0.002
Folate (ng/ml)	58.21±23.8	60.1±22.1	>0.05	56.51±17.58	70.1±16.5	0.001	0.79	<0.001
Vitamin B6 (activation coefficient)	0.59±0.46	0.59±0.45	0.18	1.16±0.43	0.80±0.40	0.001	0.18	<0.001
Vitamin B12 (ng/ml)	48.1±16.9	49.0±17.1	>0.05	46.29±11.9	60.2±12.5	0.001	0.68	<0.001
Systolic BP (mmHg)	149.2±17.55	147.1±18.1	>0.05	148.6±21.97	146.1±15.5	>0.05	>0.05	>0.05
Diastolic BP (mmHg)	80.65±9.23	80.2±8.9	>0.05	81.24±8.67	80.3±7.8	>0.05	>0.05	>0.05
Mean IMT (mm)	0.59±0.12	0.62±0.11	0.126	0.68±0.29	0.62±0.12	0.129	0.13	0.12

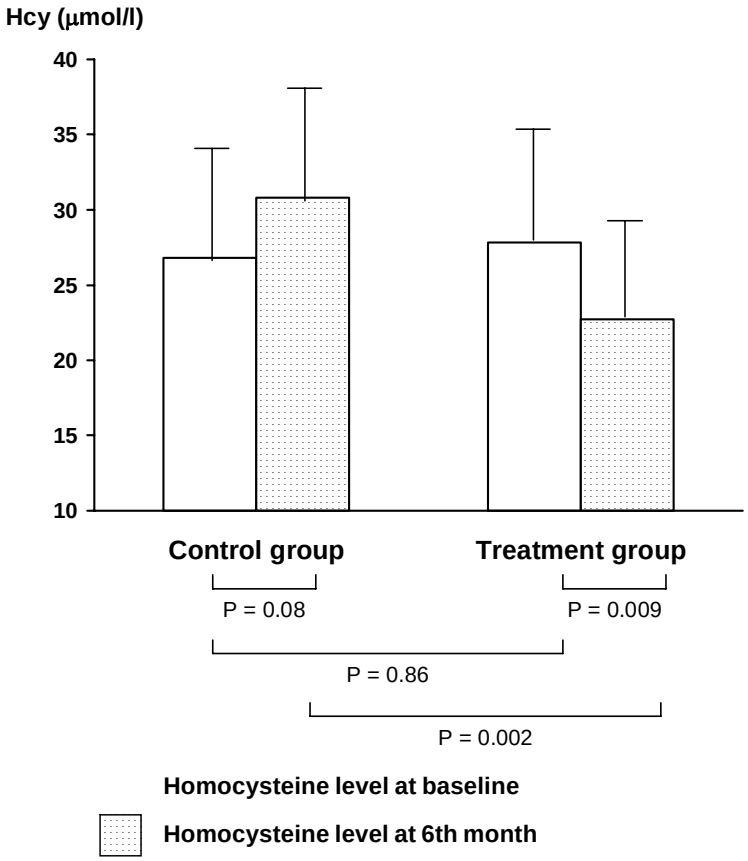

Fig. 1, 2 Changes of total homocysteine levels (mean ± SD) in the control group and the treatment group

folate doses are required for the treatment of hyperhomocysteinemia in subjects with renal failure. Two randomized trials in ESRD patients showed that 15 mg folic acid conferred an additional 15-25% reduction in total homocysteine levels compared to 1 mg folic acid[25]. Doses up to 60 mg/day were not superior in lowering total homocysteine levels compared to a dose of 15 mg/day[26]. Vitamin B12 also lowered total homocysteine with 35% in dialysis patients with low cobalamin levels[4].

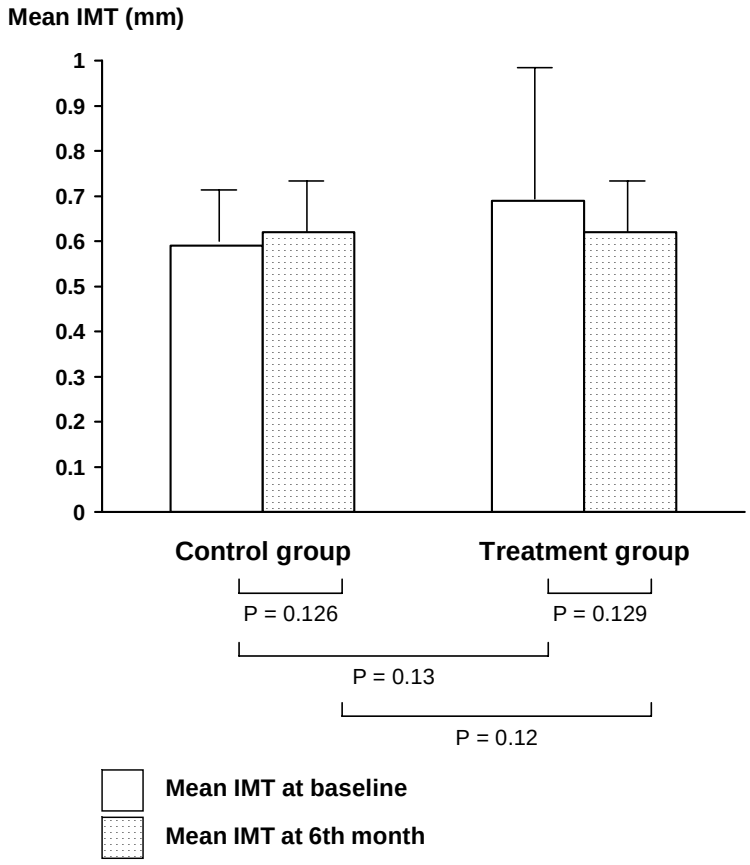

Fig. 3, 4 Changes of IMT (mean ± SD) in the control group and the treatment group

ESRD patients have accelerated atherosclerosis[27]. This was the first study of the possible effect on atherosclerosis by IMT measurement of carotid arteries. Although the present study could not demonstrate significant reduction of the arterial thickness, it might be of short duration and the very high level of homocysteine in these patients. However, it demonstrated a tendency that the treatment group had lower thickness at the sixth month (p = 0.99). Whether the normalization of hyperhomocysteinemia might be helpful in decreasing the cardiovascular morbidity and mortality in these patients requires further study.

Conclusion

The combination of folic acid 15 mg daily, 1 mg vitamin B12 and 50mg vitamin B6 reduced serum homocysteine in chronic hemodialysis patients. The long term-study of this regimen should be performed to confirm the beneficial effect on atherosclerosis.

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ผลของการให้โฟเลตและวิตะมินบี ต่อระดับโฮโมซิสเตอีน (homocysteine) และความหนาของหลอดเลือดแดงคารอติดในผู้ป่วยไตวายเรื้อรังที่ทำการฟอกเลือดด้วยเครื่องไตเทียม

ปกรณ์ ตุงคะเสรีรักษ์, ลีนา องอาจยุทธ, วลัยลักษณ์ ชัยสูตร, สมพงษ์ องอาจยุทธ, วัฒนา เลี้ยววัฒนา, สมเกียรติ วสุวัฏฏกุล, เกรียงศักดิ์ วารีแสงทิพย์, ชัยรัตน์ ฉายากุล, ทวี ชาญชัยรุจิรา, สุชาย ศรีทิพยวรรณ

วัตถุประสงค์: *ปัจจัยเสี่ยงที่สำคัญอย่างหนึ่งของภาวะหลอดเลือดแดงแข็งคือการมีระดับโฮโมซิสเตอีนสูงในเลือด ซึ่งเป็นสาเหตุของโรคหลอดเลือดแดงหัวใจตีบ โรคหลอดเลือดแดงสมอง และโรคหลอดเลือดแดงส่วนปลาย ซึ่งนำไปสู่ภาวะแทรกซ้อนจนเป็นสาเหตุการตายในผู้ป่วยไตวายเรื้อรังที่ได้รับการรักษาโดยวิธีฟอกเลือดด้วยเครื่องไตเทียม การลดระดับโฮโมซิสเตอีนสามารถลดอัตราการเกิดภาวะหลอดเลือดแดงแข็งลงได้ การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาผลของการให้ กรดโฟลิคและวิตะมินบี ว่าสามารถลดระดับโฮโมซิสเตอีน และลดหรือชะลอการเกิดภาวะหลอดเลือดแดงแข็งโดยการวัดความหนาของผนังหลอดเลือดแดงคารอติดชั้น intima ในผู้ป่วยไตวายเรื้อรังที่ทำการรักษาโดยวิธีฟอกเลือดด้วยเครื่องไตเทียมได้หรือไม่*

วัสดุและวิธีการ: *ศึกษาในผู้ป่วยจำนวน 54 คน แบ่งผู้ป่วยเป็น 2 กลุ่มโดยการสุ่ม, กลุ่มที่ 1 ได้รับกรดโฟลิค ขนาด 15 มิลลิกรัม/วัน, วิตะมินบี 6 ขนาด 50 มิลลิกรัม/วัน, และวิตะมินบี 12 ขนาด 1 มิลลิกรัม/วัน รับประทานติดต่อกันเป็นเวลา 6 เดือน, ส่วนกลุ่มที่ 2 ได้รับกรดโฟลิคขนาด 5 มิลลิกรัม/วัน*

ผลการศึกษา: *พบว่าระดับโฮโมซิสเตอีน ในกลุ่มที่ได้รับวิตะมินรวมลดลงจาก 27.94 $\pm$ 8.54 เหลือ 22.71 $\pm$ 3.68 ไมโครโมลต่อลิตร ซึ่งแตกต่างอย่างมีนัยสำคัญทางสถิติ ($p = 0.009$) ส่วนในกลุ่มที่ได้รับกรดโฟลิคอย่างเดียวมีระดับโฮโมซิสเตอีนเพิ่มขึ้นจาก 26.81 $\pm$ 7.10 เป็น 30.82 $\pm$ 8.76 ไมโครโมลต่อลิตร ซึ่งไม่มีความแตกต่างสำคัญทางสถิติ ($p = 0.08$) สำหรับค่าความหนาของหลอดเลือดแดงชั้น intima ในกลุ่มที่ได้รับวิตะมินรวมมีแนวโน้มที่จะลดลง*

สรุป: *การให้กรดโฟลิคขนาด 15 มิลลิกรัม/วัน, วิตะมินบี 6 ขนาด 50 มิลลิกรัม/วัน และวิตะมินบี 12 ขนาด 1 มิลลิกรัม/วัน สามารถที่จะลดระดับโฮโมซิสเตอีนลงได้ และมีแนวโน้มที่จะลดค่าความหนาของหลอดเลือดแดงคารอติดในผู้ป่วยไตวายเรื้อรังที่ทำการรักษาโดยวิธีฟอกเลือดด้วยเครื่องไตเทียม*