Effect of Folic Acid, Vitamin B6 and Vitamin B12 Supplementation on Mortality and Cardiovascular Complication among Patients with Chronic Kidney Disease: an Evidence-based Case Report

Alvin Nursalim[1], Parlindungan Siregar[2], Indah S. Widyahening[3]

[1] Faculty of Medicine, University of Indonesia, Jakarta, Indonesia. [2] Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia-Cipto Mangunkusumo Hospital, Jakarta, Indonesia. [3] Department of Community Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.

Correspondence mail:
Green Mansion, Jl. Green Diamond 3 no. 36, Daan Mogot, Jakarta. email: alvin.nursalim@yahoo.com.

ABSTRAK

Tujuan: *menentukan efek suplementasi asam folat, vitamin B6 dan vitamin B12 dalam menurunkan komplikasi kardiovaskular dan angka mortalitas pada penyandang penyakit ginjal kronik.* ***Metode:*** *pencarian literatur secara terstruktur dilakukan dengan menggunakan Pubmed dan Google sesuai pertanyaan klinis. Pemilihan artikel dilakukan berdasarkan kriteria inklusi dan eksklusi. Enam arikel yang terpilih kemudian dinilai kualitasnya dengan menggunakan kriteria yang mencakup validity, importance, dan applicability.* ***Hasil:*** *penggunaan asam folat dan vitamin B menurunkan kadar homosistein pada penyandang penyakit ginjal kronik. Namun, keenam studi melaporkan hasil yang seragam yaitu pemberian asam folat dan vitamin B tidak menurunkan secara signifikan komplikasi kardiovaskular dan mortalitas.* ***Kesimpulan:*** *pada penyandang penyakit ginjal kronik, pemberian asam folat, vitamin B6 dan vitamin B12 tidak menurunkan kejadian kardiovaskular dan mortalitas.*

Kata kunci: *homosistein, asam folat, vitamin B6, vitamin B12, kardiovaskular, mortalitas.*

ABSTRACT

Aim: *to determine whether the administration of folic acid, vitamin B6 and vitamin B12 would lead to reduction of cardiovascular complication and mortality among CKD patients.* ***Methods:*** *a search was conducted on PubMed and Google. The selection of title and abstract was conducted using inclusion and exclusion criterias, which led to six relevant articles. The selected studies were critically appraised for its validity, importance and applicability.* ***Results:*** *the administration of folic acid and vitamin B reduce homocysteine level among CKD patients. Despite homocysteine level reduction, all six studies reported similar findings that folic acid and vitamin B supplementation did not significantly reduce cardiovascular complication and mortality.* ***Conclusion:*** *treatment with folic acid, vitamin B6 and vitamin B12 did not reduce cardiovascular complication and mortality among CKD patients.*

Key words: *homocysteine, folic acid, vitamin B6, vitamin B12, cardiovascular, mortality.*

INTRODUCTION

Chronic kidney disease (CKD) patients usually present with high homocysteine levels. CKD patients present with hyperhomocysteinemia as a result of delayed elimination and derangement of metabolism of this metabolite. The prevalence of hyperhomocysteinemia among patients who undergoes dialysis is 80-90%, compared to 5% in the general population.[1,2]

Homocysteine is an amino acid derived from the conversion of methionine into cysteine. The participation of different cofactor/vitamins are required for its metabolization, which include: vitamin B6, vitamin B12 and folic acid. Homocysteine is suggested to cause oxidative damage to endothelial epithelium, smooth muscle proliferation and lipid peroxidation. All these events lead to atherosclerosis plaque progression.[3]

Cardiovascular complication is one of the most deadly complications among CKD patients. A cardiovascular event can be linked to CKD and the other way around. CKD is a risk factor for accelerated cardiovascular disease. Other than the classic risk factors (diabetes mellitus, high blood pressure and dyslipidemia), it is postulated that there are other novel risk factors that contribute to the increased incidence of cardiac event among CKD patients, one of which is hiperhomocysteinemia.[4] The reduction of homocysteine with vitamin B6, vitamin B12 and folic acid is well documented.[5] It was therefore logical to assume that the reduction of homocysteine by vitamins supplementation would finally lead to reduction of cardiovascular complication and mortality.

Although some studies have confirmed the association between homocysteine and cardiovascular risk, interventional studies to lower homocysteine level showed inconsistent result regarding the benefit of vitamin supplementation on clinical outcome (such as mortality and cardiac events). Despite the reduction of homocysteine level with all these agents, whether the administration of vitamin B6, vitamin B12 and folic acid lead to reduction of hard endpoints, such as mortality and cardiac event need to be further investigated.

CLINICAL QUESTION

Does the administration of vitamin B6, vitamin B12 and folic acid lead to reduction of hard endpoints, mortality and cardiovascular complication among CKD patients?

METHODS

A search of PubMed® and Google scholar® was performed on April 26th, 2012, using the key words "homocysteine", "folic acid", "vitamin B6", "vitamin B12", " cardiovascular", "mortality" and "chronic kidney diasease" along with its synonyms and related terms (**Table 1**). Search strategy, results, the inclusion and exclusion criteria are shown in a flowchart (**Figure 1**). After the selection, critical appraisal was done using several aspects based on Center of Evidence-based Medicine, University of Oxford for therapy study (**Table 2**).

Table 1. Search strategy used in PubMed and Google (Conducted on April 26th 2012)

Database	Search terms	Results
Pubmed (26th April 2012)	("homocysteine"[MeSH Terms] OR "homocysteine"[All Fields]) AND ("mortality"[Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms]) AND ("kidney failure, chronic"[MeSH Terms] OR ("kidney"[All Fields] AND "failure"[All Fields] AND "chronic"[All Fields]) OR "chronic kidney failure"[All Fields] OR ("chronic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "chronic kidney disease"[All Fields])	186
Google scholar (26th April 2012)	homocystein, mortality and chronic kidney diasease	10

RESULTS

From the selection and filtration, six articles qualified for further assessment. These articles were appraised and considered to have a good validity and relevance. All studies are randomized trial with similar characteristics

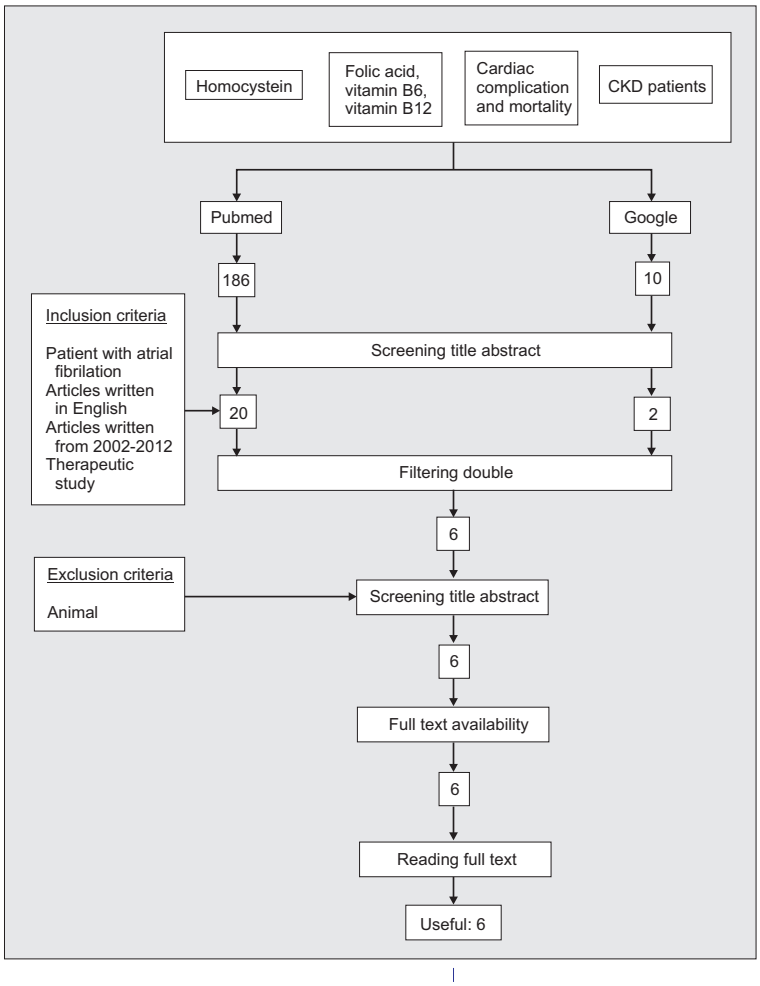

Figure 1. Flow chart of search strategy

between intervention group and control group. Heinz J et al[7] studied whether homocysteine reduction by folic acid, vitamin B6 and vitamin B12 would lead to reduction of mortality among end stage renal disease (ESRD) patients who underwent hemodyalisis. The intervention was 5 mg folic acid, 50 µg vitamin B12, and 20 mg vitamin B6 (in the active treatment group) or 0.2 mg folic acid, 4 µg vitamin B12, and 1.0 mg vitamin B6 (in the placebo group) given 3 times per week for an average of 2 years. There was no significant difference in terms of total mortality between the two groups. Total mortality occurred in 102 patients (31%) receiving the active treatment and in 92 patients (28%) receiving placebo (hazard ratio, 1.13; 95% confidence interval, 0.85 to 1.50; p=0.51). The analysis of secondary outcome (cardiovascular events) also revealed similar finding. There was no significant difference in terms of cardiovascular event between these two groups (hazard ratio, 0.80; 95% confidence interval, 0.60 to 1.07; p=0.13).

The second articles by Jamison RL[8] also conducted a study among ESRD patients. Other inclusion criterias include patients with estimated creatinine clearance ≤30 ml/min and plasma homocysteine level of 15 µmol/L or higher. Participants received a daily capsule containing 40 mg of folic acid, 100 mg of vitamin B6 and 2 mg of vitamin B12 or a placebo. After a median follow up of 3.2 years, statistical analysis was performed for mortality, myocardial infarction (MI) and stroke. Mortality occured in 448 patients in the vitamin group and in 436 in the placebo group (hazard ratio, 1.04; 95% CI, 0.91-1.18; p=0.60). There was also no significant effects for MI and stroke. There were 129 MIs in the vitamin group and 150 in the placebo group (hazard ratio, 0.86; 95% CI, 0.67-1.08), 37 patients had strokes in the vitamin group and

Table 2. Critical appraisal of the 6 useful articles based on criterias by Centre of Evidence Medicine University of Oxford[6]

Articles	Validity							Relevance			Result	Levels of evidence
	study design	number of patients	randomization	similarity treatment and control	blinding	comparable treatment	intention to treat	domain	determinant	measurement of outcome		
Heinz J et al[7]	+	650	+	+	+	+	+	+	+	+	A	1B
Jamison RL et al[8]	+	2056	+	+	+	+	+	+	+	+	B	1B
Mann JFE[9]	+	619	+	+	+	+	+	+	+	+	C	1B
Wrone EM[10]	+a	510	+	+	+	+	+	+	+	+	D	1B
Bosto m AG[11]	+	4110	+	+	+	+	+	+	+	+	E	1B
Zoungas S[12]	+	315	+	+	+	+	+	+	+	+	F	1B

+ stated clearly in the article; - not being done; ? not stated clearly; *Levels of evidence based on The Oxford Centre of Evidence-based Medicine; a: This is a randomised trial with three treatment groups (1, 5, or 15 mg of folic acid)
A. Total mortality occurred in 102 patients (31%) receiving the active treatment and in 92 (28%) receiving placebo (hazard ratio, 1.13; 95% confidence interval, 0.85 to 1.50; P=0.51); B. Mortality occured in 448 patients in the vitamin group and in 436 in the placebo group (hazard ratio, 1.04; 95% CI, 0.91-1.18; P=0.60); C. Active treatment lowered homocysteine levels in participants with CKD but did not reduce cardiovascular risk (relative risk, 1.19; 95% confidence interval, 0.88–1.61; P=0.25); D. Composite rates of mortality and cardiovascular events among the folic acid groups did not differ at 24 months (43.7% in 1 mg group, 38.6% in 5 mg group, 47.1% in 15 mg group; log-rank P=0.47); E. Treatment with high dose multivitamin reduced homocysteine level but did not significantly reduce primary cardiovascular outcome (hazard ratio 1.01, 95% confidence interval 0.86 to 1.19, P=0.91) and all cause mortality (hazard ratio 1.06, 95% confidence interval 0.89 to 1.27, P=0.50); F. High-dose folic acid does not improve cardiovascular mortality in patients with chronic kidney disease (hazard ratio 0.93, 95% confidence interval 0.58-1.48, P=0.75).

41 had stroke in the placebo group (hazard ratio, 0.90; 95% CI, 0.58-1.40).

The third study by Mann JFE et al.[9] studied the effiacy of administration of 2.5 mg folic acid, 50 mg vitamin B6 and 1 mg vitamin B12 in reducing composite death from cardiovascular causes, myocardial infarction or stroke. A total of 619 patients age 55 or older with an estimated glomerular filtration rate (eGFR) <60 ml/minute were randomized to either active treatment or placebo. After 5 years follow up, despite adequate reduction of homocysteine to 11.9±3.3 µmol/l in the active group, there is no significant differences in the composite death between both groups (relative risk, 1.19; 95% confidence interval, 0.88–1.61; p=0.25).

In a 24 month randomized trial among 510 patients with end stage renal disease undergoing dialysis, Wrone EM et al.[10] studied the efficacy of different doses of folic acid on top of other vitamins (among of which are 12.5 mg of vitamin B6 and 6 µg of vitamin B12, 60 mg of ascorbic acid, 1.5 mg of vitamin B1, 20 mg of vitamin B3, 10 mg of vitamin B5, and 0.3 mg of vitamin B7). In those treated with high dose of folic acid (15 mg folic acid) there was 61 death versus 56 death in he low dose group (1 mg of folic acid). The composite mortality did not differ at 24 months (43.7% in 1 mg group, 38.6% in 5 mg group, 47.1% in 15 mg group; log-rank *p*=0.47).

In a 5 year randomized controlled trial involving 4110 kidney transplant recipients, Bostom AG et al.[11] studied the efficacy of 5 mg folic acid, 50 mg vitamin B6 and 1.0 mg vitamin B12 for cardiovascular event reduction and mortality reduction. The comparison group received no folic acid, 1.4 mg vitamin B6 and 2.0 vitamin B12. Treatment with high dose multivitamin reduced homocysteine level but did not significantly reduce primary cardiovascular outcome (hazard ratio 1.01, 95% confidence interval 0.86 to 1.19, p=0.91) and all cause mortality (hazard ratio 1.06, 95% confidence interval 0.89 to 1.27, p=0.50).

Zoungas S[12] studied the efficacy of 15 mg folic acid administration as compared to placebo among 315 subjects with creatinine clearance <25ml/minute in reducing cardiac event and mortality. After a mean follow up of 36 months, the level of homocysteine reduced to 21.5 µmol/L in the folic acid group as compared with 23.9 µmol/L in the placebo group. There

was no significant differences in terms of first myocardial infarction, stroke or death from cardiovascular cause (Hazard ratio 0.93, 95% confidence interval 0.58-1.48, p=0.75).

DISCUSSION

The association between high homocysteine levels and cardiovascular disease has been studied in numerous studies.[3,13] On the other hand, homocysteine can also be lowered by folic acid and vitamin B supplementation.[5] Therefore, it is logical to assume that homocysteine-lowering by vitamins administration would reduce cariovascular complication and would finally reduce mortality.

This review comprised of six studies with varying patient characteristics and different vitamin dose. The participant on two studies were end stage renal disease (ESRD) patients on hemodyalisis, the participant in one study were kidney transplant recipients and the participant in the remaining three studies were CKD patients on varying stage. Most studies used folic acid, vitamin B6 and vitamin B12 as their intervention, while on one study, the intervention was folic acid with varying doses.

As might be expected, baseline homocysteine level are highest among patients with ESRD. (the online table, www.inaactamedica.org/archives/2013/appendix/nursalim_vol45-p.150.pdf). Homocysteine level is inversely related to renal function.[1] This observation might resulted from impaired secretion or metabolism. Nevertheless, all study population reported homocysteine reduction with folic acid and vitamin B supplementation.

Despite adequate reduction of homocysteine level in most studies (online table, www.inaactamedica.org/archives/2013/appendix/nursalim_vol45-p.150.pdf), all studies reported similar finding that folic acid, vitamin B6 and vitamin B12 administration did not significantly reduce the occurence of cardiovascular complication and mortality among patients with chronic kidney disease, even in some cases, it increased the risk of having cardiac complication and mortality. As summarized in the online appendix, some studies reported insignificant slight reduction in terms of cardic complication (relative risk reduction: 13-17%) but then the other reported insignificant increased of mortality. All studies reported mortality increase in the vitamin group (relative risk increase: 2-11%). This similar result might indicate the possible harm of vitamin supplementation. Please keep in mind that these results were not statistically significant so this conflicting result should be intepreted with caution. So, until another clinical trial with better method and larger amount of participant can conclude this, all existing studies in this review failed to demonstrate any concrete benefit of vitamin supplementation.

As explained in previous paragraph, all studies reported no significant benefit in regards of cardiovascular complication and mortality. This finding might be in contrast to common belief that homocysteine reduction would lead to reduction of cardiovascular event and mortality. It is not useful to know that the study participant in all these studies were randomized whether to be allocated in the intervention or placebo group. Thus, both groups had an event and comparable characteristics in every study. The baseline characteristics (including risk factors) of both group were also shown in most studies, which were, once again, comparable. This fact needs to be emphazised because one could argue that the negative findings of these studies were due to the discrepancies of the participant characteristics between the intervention and the placebo group, and that's not the case in this review.

There are some possible reasons behind this uniform negative result. First, homocysteine level is not related to any vascular damage in CKD patients at all. The relationship between the high incidence of cardiovascular complication among CKD patients might related to other factors outside homocysteine level. The mechanism for this relationship needs to be further studied and are likely independent of homocysteine level. Second, the length of follow-up might not be sufficient to prove any beneficial effect of homocysteine lowering by all these supplementations. In a study by Jamison RL[8], it was reported that only one third of the study participants achieved the normal homocysteine target, despite administration of the highest vitamin doses among homocysteine

lowering studies reported to date. This fact could partially contribute to the negative finding in this particular study.

Another important point to note is the possibility of adverse effect of vitamin supplementation. Vitamin supplementations might pose detrimental effect on patients that offset its homocysteine-lowering benefit, as documented in some studies.[14] Although there were no serious adverse events related with folic acid and vitamin B supplementation in these studies, Bonaa KH et al. (NORVIT trial)[15] reported the tendency of increased cardiovascular event among those patients taking folic acid and vitamin B supplementations. This study also reported an inreased risk of cancer event in the folic acid group (not statistically significant). Nevertheless, this side effect issue is still not settled and there is currently no study reported the exact relationship between vitamin supplementation and cancer incidence.

Despite all these negative findings among CKD patients, homocysteine lowering might be beneficial for a different population. One of the population that might be benefited by folic acid and vitamin B supplementation is patients with inborn error metabolism, cystathionine β synthetase deficiency. In this population, the homocysteine level was very high (150 µmol/L), as compared with the homocysteine level in the range of 10-25µmol/L in most of these studies. This population whose homocysteine level is markedly elevated gain beneficial effects from homocysteine lowering treatment.[16]

The limitation of this review is the lack of an Asian-population based studies. As there might be a difference of homocysteine levels among certain ethnic groups.[17] An even ethnic distribution is important if the recommendation from this study is to be implemented in all ethnic group. Future studies with larger amount of participants, more widespread population and longer follow up will hopefully clarify the significance of homocysteine-lowering treatment in CKD patients. As clinicians, we should give more emphasis on clinical endpoint, not surrogate markers (in this case homocysteine level). So in the meantime, based on existing studies, there is not enough evidence to justify routine use of homocysteine-lowering supplements among CKD patients.

CONCLUSION

The administration of folic acid, vitamin B6 and vitamin B12 reduced homocysteine level but did not reduce cardiovascular event and mortality among CKD patients. Based on this appraisal, we do not recommend the routine use of homocysteine-lowering supplements among CKD patients.

The result of this appraisal can be applied in clinical practise. For example, this case is presented to us. A 56 years old man was diagnosed with type 2 diabetes mellitus, hypertension and chronic kidney disease stage 3. According to physical examination, the patient was in a good condition except his blood pressure was 150/100 and there was no diabetic complication observed. The laboratory findings were all within normal range, including lipid profile (total cholesterol, tryglyceride, LDL and HDL) except anemia (Hb: 9,5 mg/dl) and elevated creatinine level (1.8 gr/dl). Homocysteine was not meassured in this routine laboratory examination. There were no abnormalities found on the X-ray and electrocardiography examination. Beside the regular prescriptions of oral diabetic medication and antihypertensive regimens, the doctor considered to administer folic acid, vitamin B6 and vitamin B12. Since there was no sufficient evidence that support the benefit of homocysteine lowering by folic acid and vitamin B supplementation among CKD patients, the doctor decided not to prescribe all these vitamins for this patient.

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