Research Article

Safety and effectiveness of intravenous vitamin B combination in chronic kidney disease patients with hyperhomocysteinemia

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Abstract

Background: Hyperhomocysteinemia may be associated with increased morbidity and mortality from cardiovascular disease in chronic kidney disease (CKD) patients. Previous study stated vitamin B supplementation effectively reduce homocysteine levels. **Objective:** This study aimed to identify the safety and effectiveness of intravenous vitamin B combination to reduce homocystein level in patients with CKD. **Material and Methodss:** This was an observational non control study. Subjects were male or female, >18 years, and has a CKD with a routine hemodyalisis two times per week. Every subject has a routine vitamin B combination injection. The vitamin B combination consist of 100 mg vitamin B1, 100 mg vitamin B6, and 5000 mcg vitamin B12. It injected intravenously after each hemodyalisis. The shifting of homocysteine level from the first week to the second week described as delta (Δ) homocysteine. **Results:** Homocysteine level was measured at baseline, second, and fourth week. The percentage of hyperhomocysteinemia and the mean of homocysteine level were decreasing from baseline (89.3%; mean 23.43±8.39 μmol/L) to the last visit (20.5%; mean 12.24±4.41 μmol/L). A significant reduction was seen in Δ homocysteine 1-2 (p:0.009) and Δ homocysteine 1-4 (p:0.008). Observasion of adverse event was made at the second and the fourth week. There were two subjects who had an adverse event during this study at the second week. After a further investigation, the adverse events concluded to be not correlate to the administration of intravenous vitamin B combination. **Conclusion:** Vitamin B combination proven to be effective and safe to reduce the homocysteine level in CKD patients.

***Keywords**:* chronic kidney disease, hemodyalisis, homocysteine, vitamin B

Introduction

Chronic kidney disease (CKD) is a common disease in Indonesia. The prevalence of CKD in Indonesia is increase from 2.0 ‰ in 2013 to 3.8 ‰ in 2018 (Ministry of Health Republic of Indonesia, 2018). The number of new hemodyalisis patients in Indonesia increase consistently from 2013 to 2017 (Indonesian Nephrology Association, 2010). In 2018, the proportion of CKD patients with hemodyalisis is 19.3 % (Ministry of Health Republic of Indonesia, 2018). CKD leads to poor outcomes and high costs in Indonesia. According to data from national insurance system, CKD is the third leading cause of catastrophic disease in Indonesia (Sarnak et al., 2003).

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Cardiovascular disease (CVD) and stroke are the most common cause of death in the setting of end-stage renal disease (Collins et al., 2014). Individuals with CKD are more likely to die of CVD than from the progress of the disease itself (McCullough et al., 2011). Hyperhomocysteinemia is present in the majority of CKD patients and among patients undergoing hemodialysis (Danis et al., 2008). The prevalence of hyperhomocysteinemia is over 80% among dialysis patients (Turner et al., 2011). Hyperhomocysteinemia appears to be associated with increased cardiovascular disease risk (Tamadon et al., 2011; McNulty and Scott, 2008). In the general population, hyperhomocysteinemia is commonly associated with deficiencies in a folic acid and vitamin B. Vitamin B and folate supplementation effectively reduce homocysteine levels in the general population (Turner et al., 2012).

Vitamin B is one of the most frequent supplementation among CKD patients (Amini et al., 2015; Steiber and Kopple, 2011). The use of intravenous vitamin B

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combination is a common practice in hemodialysis unit at Bethesda Hospital and Panti Rapih Hospital, Yogyakarta, Indonesia. Unfortunately, study focused on hyperhomocysteinemia and the benefit of vitamin B combination to reduce homocysteine level in patients with CKD in Indonesia is very limited. The safety profile of intravenous vitamin B combination is also under-reported. We hypothesize intravenous vitamin B will reduce by the mean homocysteine level 5 µmol/L after 4 weeks treatment and homocysteine level will be normal in 60% of patients after the administration compared with 40% patients before the administration. This study aimed to identify the effectiveness of intravenous vitamin B combination to reduce homocystein level in patients with CKD and evaluate the safety profile of intravenous vitamin B combination.

Materials and methods

Research design

This was an observational non control study. This study was conducted at Bethesda Hospital and Panti Rapih Hospital, Yogyakarta, Indonesia from August to October 2018. Each subject would be followed for 4 weeks. Figure 1 below describes the study process.

Subjects selection selection

The minimum subject requirement were 120 subjects. The inclusion criteria i.e.: male or female, age >18 years, and has a CKD with routine hemodyalisis, two times per week. The interval between each hemodyalisis was 3 to 4 days. Every subject who: does not willing to join the study, has a known hypersensitivity to vitamin B combination or its composition, participation in other clinical trial in the last 1 month, incompetent to give a consent and to answer the questionnaires, pregnant or has a plan to get pregnant was excluded.

Every subject was given an intravenous vitamin B combination. The vitamin B combination consist of 100 mg vitamin B1, 100 mg vitamin B6, and 5000 mcg vitamin B12. It injected intravenously after each hemodyalisis. During this study, subjects did not allow taking other supplementation of vitamin B. Subject who has a history of routine vitamin B combination supplementation was allowed to join this study after 1 week washout. Every subject who fulfilled the criteria was asked to sign an informed consent form.

Assessment of Assessment of Variables

The duration of observation was 4 weeks. Variables assessed in this study i.e.: demographic data, medical history, co-treatment, homocysteine level, and the presence of adverse event. Demographic data includes age, gender, marriage status, educational degree, occupation, type of health financing, and ethnicity.

The homocysteine level and hematology parameter measured at the baseline/first week (before the first hemodyalisis), second week (after the second hemodyalisis), and fourth week (after the second hemodyalisis). About 5 ml venous blood was collected at each measurement. The process of blood drawing was done by nurse in hemodyalisis center and tested by laboratory technician. The blood was stored into 2 different tubes: one tube contains ethylene-diamine-tetraacetic acid (EDTA) and other tube contain clot activator. Blood collected in tube with EDTA will be processed for hematology parameter, whereas blood collected in tube with clot activator will be processed for homocysteine level. Hyperhomocysteine defined as homocysteine level higher than 15.39 µmol/L.

Statistical Analysis

Univariate analysis used to determine the characteristics of subjects. Bivariate analysis was using a chi square test to identify the significant variable(s) to hyperhomocysteinemia status on the fourth week. Every significant variable(s) will be analyzed further using repeated measures analysis. The significance of homocysteine level reduction was analyzed using paired T test or Wilcoxon test. The shifting of homocysteine level describe delta (Δ) homocysteine 1 – 2 and Δ homocysteine 1 – 4. Delta homocysteine 1 – 2 obtained from subtraction between homocysteine level at the baseline and homocysteine level at the second week, whereas delta homocysteine 1 – 4 obtained from subtraction between homocysteine level at the baseline and homocysteine level at the fourth week The significant level was set at $p < 0.05$.

Research Ethics

This study uses a primary data in subjects. Therefore, informed consent process will be made very clearly. Patients are freed to choose to be involved or not involved in this study. For those who refuse to be involved in this study are not required to explain their reason and will not affect their therapy. Every subject would be given the results of blood tests.

The data used only for the purpose of research. Patients identity, such as name and address, will be classified. All document will be saved in research site after the research is completed. The research document will only be seen by the parties related to this research. This study was verified by Duta Wacana Christian University School of Medicine Ethical Research Committee. The number of ethical clearance was 614/C.16/FK/2018.

Results

Total subject at the baseline was 122. Four subject could not continue the study at the second week: 1 subject was loss to

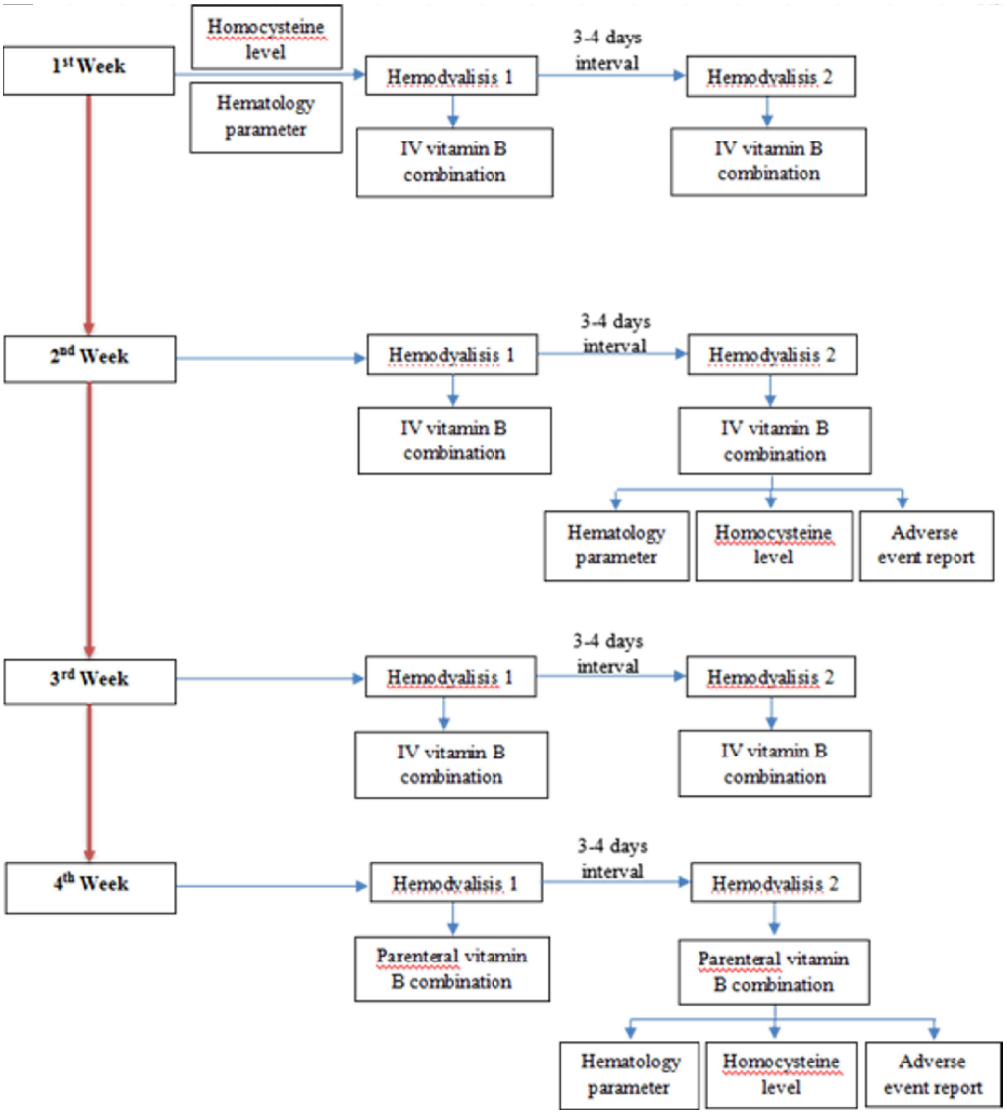

Figure 1. The study process

follow up, 1 subject was not well-being and need to be hospitalized, 1 subject exclude due to blood sample lysis, and 1 subject died due to metabolic complications. At the fourth week, one more subject was loss to follow up. The number of subject who took part until the last week was 117.

Table 1 showed the characteristics of the subjects. Subjects was dominated by male (63.9%) with mean age 51.67 years. The most common comorbidity was anemia (86.9%) and followed by hypertension (86.1%). Folic acid (86.1%), hematopoietic agent (82.8%), and anti hypertensive drug (82%) were the common co-treatment during this study.

Homocysteine level was measured three times: at the baseline, second week, and fourth week. The percentage of hyperhomocysteinemia and the mean of homocysteine level were decreasing from the baseline to the last visit as shown in table 2 and figure 2. A significant reduction was seen in Δ homocysteine 1 - 2 (p: 0.009) and Δ homocysteine 1 - 3 (p: 0.008).

Bivariate analysis was done to identify any significant variable(s) to the presence of hyperhomocysteinemia at the fourth week. Table 3 summarized the result of bivariate analysis. Gender, comorbidity including; congenital kidney disease and urinary tract infection, and also medication including folic acid and anti hypertensive drug had a

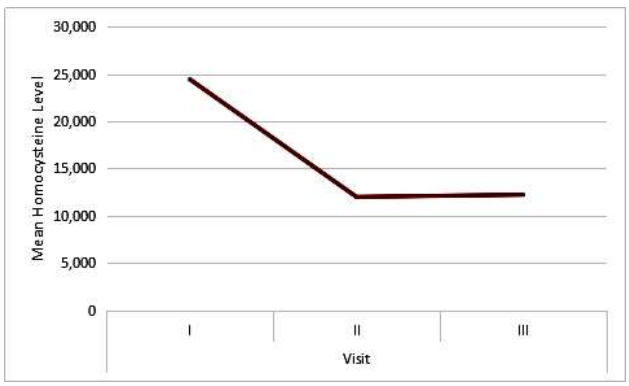

Figure 2. Mean homocysteine level

Table 1. Characteristics of subjects at baseline

Parameters	Characteristics	Number (n: 122)	%
Gender	Male	78	63.9
	Female	44	36.1
Age (mean)		51.67 ± 12.61 years	
Comorbidity	Hypertension	105	86.1
	Diabetes Mellitus	41	33.6
	Stroke	9	7.4
	Cardiovascular disease	32	26.2
	Congenital kidney disease	2	1.6
	Urinary tract calculus	9	7.4
	Urinary tract infection	5	4.1
	Anemia	106	86.9
	Dyslipidemia	4	3.3
Co-treatment	Folic acid	105	86.1
	Calcium carbonat	84	68.9
	Antihypertensive drug	100	82
	Antidiabetic drug	27	22.1
	Antiplatelet	11	9.0
	Lipid lowering drug	7	5.7
	Hematopoietic agent	101	82.8

Table 2. The prevalence of hyperhomocysteinemia and mean homocyteine level

Visit (Total Subjects)	Prevalence of Hyperhomocysteinemia (%)	Mean Homocysteine Level (µmol/L)
First Week (n = 122)	109 (89.3)	23.43 ± 8.39
Second Week (n = 118)	20 (16.9)	12.01 ± 3.77
Third Week (n = 117)	24 (20.5)	12.24 ± 4.41

significant result ($p < 0.05$). Further analysis of these variables was performed. Further analysis on congenital kidney disease, urinary tract infection, folic acid, and anti hypertensive drug indicated these variables was not significant, whereas gender was significant to homocysteine level (p : 0.009).

Observation of adverse event was made at the second and the fourth week. There were two subjects who had an adverse event at the second week. These subjects had a history of recurrent dyspnea before this study began. The first subject diagnosed with acute lung edema at the second week of study. This subject needed to be hospitalized and the frequency of hemodyalisis changed to three times per week. The second subject died at the second week of study due to metabolic complication; lung edema and hypoglycemia. Each subject has been treated in the study center. Further investigation was done to determine the correlation of these events and the administration of intravenous vitamin B combination. There was no correlation between these adverse events with the administration of vitamin B combination.

Table 3. Bivariate Analysis

Variables		Visit III (n: 117)		p
		With Hyperhomo-cysteinemia n (%)	Without Hyperhomo-cysteinemia n (%)	
Age (mean)		51.17 ± 12.53	51.69 ± 12.57	0.632
Gender:				
Male		16 (13.7)	57 (48.7)	0.035
Female		8 (6.8)	36 (30.8)	
Comorbidities : Hypertension		18 (15.4)	83 (70.9)	0.070
	Diabetes Mellitus	10 (8.5)	30 (25.6)	0.386
	Cardiovascular Disease	3 (2.6)	28 (23.9)	0.081
	Stroke	1 (0.9)	7 (6.0)	0.561
	Congenital Kidney Disease	2 (1.7)	0 (0)	0.005
	Urinary Tract Calculus	2 (1.7)	7 (6.0)	0.895
	Anemia	20 (17.1)	81 (69.2)	0.632
	Dyslipidemia	1 (0.9)	3 (2.6)	0.821
	Urinary Tract Infection	3 (2.6)	2 (1.7)	0.025
Medication	Folic Acid	18 (15.4)	84 (71.8)	0.045
	Calcium Carbonat	17 (14.5)	65 (55.6)	0.928
	Anti Hypertensive Drug	15 (12.8)	81 (69.2)	0.005
	Anti Diabetic Drug	7 (6.0)	20 (17.1)	0.427
	Anti Platelet Drug	0 (0)	11 (9.4)	0.077
	Lipid Lowering Drug	0 (0)	6 (5.1)	0.201
	Hematopoetic Agent	18 (15.4)	79 (67.5)	0.249

Table 4. Repeated Measure Analysis

Variables	p
Gender	0.009
Congenital Kidney Disease	0.569
Urinary Tract Infection	0.438
Folic Acid	0.548
Anti Hypertensive Drug	0.219

Table 5. The prevalence of adverse event

Visit	Adverse Event (%)	Description	Relation to Medication
Second Week	2 (1.6)	Metabolic complication	Unrelated
Fourth Week	0 (0)	-	-

Discussion

Homocysteine is a sulfur amino acid. It is the only direct precursor for l-methionine synthesis through a reaction that requires vitamin B (Manolescu et al., 2010). The elevation of homocysteine level in blood above the normal level referred as hyperhomocysteinemia. The prevalence of hyperhomocysteinemia is higher among CKD patients (Maron and Loscalzo, 2009). One of the proposed

mechanisms is due to 70% of homocysteine is excreted through kidney (Suwanto, 2017; Ciancolo et al., 2017). A comparative cross-sectional study among 138 patients with CKD and 69 healthy consenting hospital staff individuals showed the prevalence of hyperhomocysteinemia was 57.9% among cases and 4.3% among control subjects with median homocysteine level being 19.1 µmol/l in cases and 8.3 µmol/l in controls, this was significant ($p < 0.001$) the chronic kidney disease patients having higher median homocysteine levels as the degree of kidney disease worsened (Olokor et al., 2016). A randomized placebo-controlled trial on 100 cases also showed serum homocysteine is elevated in patients of CKD (Nand et al., 2013). The result in this current study is similar to previous study, the prevalence of hyperhomocysteinemia at the baseline was high (89.3%) with mean homocysteine level was 23.43 ± 8.39 µmol/L.

Metabolism of homocysteine is mostly dependent on folic acid (vitamin B9), vitamin B12, and vitamin B6 serum levels (Markisic et al., 2017; Loland et al., 2010), therefore vitamin B is one of medication in hyperhomocysteinemia. Vitamin B6 is mainly important in the decrease of the homocysteine levels after methionine loading. Daily vitamin B12 intake of at least 0.4 mg makes the level drop further with 7% and a daily folic acid intake of 0.5 to 5 mg, makes the plasma homocysteine level drop with about 25% (Terwecoren et al., 2009). Research on patients with vascular disease with daily treatment combination of 2.5 mg of folic acid, 50 mg of vitamin B6, and 1 mg of vitamin B12 or with a placebo for an average of five years revealed mean plasma homocysteine levels decreased by 2.4 µmol per liter (0.3 mg per liter) in the active-treatment group and increased by 0.8 µmol per liter (0.1 mg per liter) in the placebo group (The Heart Outcomes Prevention Evaluation 2, 2006).

Current study was using vitamin B combination consist of 100 mg vitamin B1, 100 mg vitamin B6, and 5000 mcg vitamin B12. After 4 weeks administration of vitamin B combination, the prevalence of hyperhomocysteinemia decrease significantly from 89.3% at the baseline to 20.5% at the fourth week. This reduction is statistically significant (p: 0.008). Hyperhomocysteinemia was common in male subject (30.7%). From bivariate analysis, gender, congenital kidney disease, urinary tract infection, administration of folic acid, and anti hypertensive drug were significant to hyperhomocysteinemia at the fourth week. Further analysis using repeated measure analysis proved a significant difference on homocysteine level between the gender (p: 0.009). Other variables, such as comorbidities and other medication, were not significant to homocysteine level.

Hyperhomocysteinemia increases the likelihood of stroke (Markisic et al., 2017) and cardiovascular disease (Maron and Loscalzo, 2009; Loland et al., 2010; Veeranna et al., 2011). From a genetic and prospective studies by Debreceni et al., it has been concluded that a 3 lmol/L decrease in serum homocysteine lowers the risk of myocardial infarction and stroke by 15% and 24%, respectively (Debreceni B and Debreceni L, 2014). From other study, each 5 lmol/L increase in Hcy level increases the risk of coronary heart disease (CHD) events by approximately 20%, independently of traditional CHD risk factors (Humphrey et al., 2008). Study by Nand, et al. revealed the opposite result. Folic acid and vitamin B12 supplementation lowered homocysteine, but it did not reduce cardiovascular disease mortality (Nand et al., 2013). Saposnik et al. (2009) states lowering of homocysteine with folic acid and vitamins B6 and B12 did reduce the risk of overall stroke, but not stroke severity or disability. The correlation between homocystein reduction and cardio/cerebrovascular risk apparently not yet concluded. Current study was not followed prospectively to find out this correlation. Future study in this topic is necessary.

Hyperhomocysteinemia exerts its pathogenic action on the main processes involved in the progression of vascular damage already enhanced in CKD patients. Hyperhomocysteinemia induces oxidative stress and antagonizes the vasodilator properties of nitric oxide (Ciancolo et al., 2017). It is leading to endothelial cell injury and thereby initiates the process of premature atherosclerosis (Terwecoren et al., 2009). Following oxidative injury, endothel cell apoptosis and induction of protrombotic environment by increasing platelet aggregasion and vascular inflammation (Suwanto, 2017). Hyperhomocysteinemia is also accompanied by a hypercoagulable state. Hyperhomocysteinemia has been associated with impaired fibrinolysis, leads to alteration of fibrin clot structure and affects fibrin clot resistance to lysis in human subjects. As thrombosis plays an important role in plaque development and acute coronary syndromes, hyperhomocysteinemia may increase cardiovascular risk by increasing the thrombotic potential (Debreceni and Debreceni, 2014).

Vitamin B considered a safe medication. Vitamin B is one of the most frequent supplementation among CKD patients (Aini et al., 2015; Steiber and Kopple, 2011). The result of HOPE-2 study, a randomized, double-blind, placebo-controlled trial, which evaluated the effects of homocysteine-lowering B vitamins on major vascular events in a high-risk population (n = 5522), showed there were no serious adverse events related to study treatment (Mann et al., 2008). Study in India found there was no adverse effect observed due to folic acid and vitamin B12 and B6 therapy during the follow-up period (Nand et al., 2013). An evidence-based case report by Nursalim et al. (2013) conclude there were no serious adverse events related with folic acid and vitamin B supplementation.

Administration of intravenous vitamin B combination proved to be safe in this study. There was no side effect due to administration of intravenous vitamin B combination. Two

adverse events in this study were not related to vitamin B combination. It caused by the underlying disease.

To our knowledge, this was the first study in Indonesia that concerned on homocysteine level and vitamin B combination. Many previous studies were using combination of folic acid, vitamin B6, and vitamin B12 in hyperhomocysteinemia but not vitamin B1. Future study with larger sample number and followed prospectively to find out the correlation between homocysteine level, administration of vitamin B combination, and the risk of cardio/cerebrovascular disease is needed.

Conflict of interest

There is no conflict of interest.

Conclusion

Vitamin B combination, consist of 100 mg vitamin B1, 100 mg vitamin B6, and 5000 mcg vitamin B12 proven to be effective at reducing the homocysteine level in CKD patients. Administration of the medication by intravenous is safe, without any serious side effect. The usage of intravenous vitamin B combination should be used widely in every CKD patients who are undergoing hemodyalisis.

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