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The Benefit and Safety of Vitamin B Combination to Reduce Fatigue and Improve Quality of Life in Chronic Kidney Disease Patients

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ABSTRACT

Background: Chronic kidney disease (CKD) patients often have a chronic fatigue and lower QoL, thus may increase morbidity and mortality in CKD patients. **Objective:** The objective was to identify the benefit and safety of administration of intravenous vitamin B combination to reducing fatigue, measure the prevalence of fatigue and QoL in CKD patients. **Method:** This study was an observational non control study for 4 weeks in CKD patients with routine hemodyalisis 2 times/week. Every subject has a routine administration of intravenous vitamin B combination, consist of 100 mg vitamin B_1, 100 mg vitamin B_6, and 5000 mcg vitamin B_{12}, after each hemodyalisis. Visual analogue scale (VAS) used to measure the degree of fatigue. QoL measured using SF-8 questionnaire, consist of total, physical (PCS), and mental component (MCS). **Results:** The prevalence of fatigue is high. The mean VAS score was 3.4±2.1 at baseline and there were 46.7% subjects with VAS score above the mean VAS score. After 4 weeks administration of vitamin B combination intravenously, the mean VAS score was decreasing from 3.4 to 2.7. The prevalence of fatigue was decreasing from 46.7% to 41%. This shifting was statistically significant (p:0.008). There was a score reduction in total component (20.19±4.8 to 19.29±4.9), PCS (13.44±3.1 to 12.99±3.5), and MCS (6.75±2.1 to 6.31±1.9). This score reduction indicated a better QoL. However, the reduction was not statistically significant. **Conclusion:** The prevalence of fatigue is high. Intravenous vitamin B combination considered to be effective and safe to reducing the degree of fatigue in CKD patients.

Keywords: chronic kidney disease, fatigue, hyperhomocysteinemia, vitamin B combination, quality of life

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INTRODUCTION

There is increasing awareness of the high symptom burden and impaired health related quality of life (QoL) experienced by patients with chronic kidney disease (CKD).[1] Patients with CKD often experience a wide variety of symptoms as disease progresses.[2] Patients with routine hemodyalysis often accompanied by various symptoms such as fatigue, pain, muscle cramps, difficulty with sleep, and sexual dysfunction.[3] Fatigue is one of the most prevalent symptoms in CKD with dyalisis.[4,5] Fatigue defined as a complex, multidimensional, and multifactorial phenomenon, which has been defined as 'extreme and persistent tiredness, weakness or exhaustionmental, physical or both'.[6] According to Gordon, et al. (2011) approximately 86% of patients experience postdialysis fatigue ranging from mild-to-severe.[7]

Chronic fatigue impacts patients' daily functioning, QoL, and delays recovery after hemodialysis.[8] Fatigue has been associated with increases the risk of cardiovascular events, negatively influences survival, and increased risk for mortality in hemodialysis patients.[8-10] Very little data are available concerning the QoL of patients with end-stage renal disease maintained on dialysis in the developing world.[11] Therefore, it is important to delve deeper into this topic.

Vitamin deficiencies, such as vitamin B_1, vitamin B_6, and vitamin B_{12}, are common in people with advanced renal failure who do not take nutritional supplements and may be the cause of fatigue in CKD patients.[11]

OBJECTIVES

The main objective of this study is to identify the benefit of intravenous vitamin B combination to reduce fatigue in CKD

patients. The secondary objective is to measure the prevalence of fatigue and QoL in CKD patients. This study also identify the safety of intravenous vitamin B combination in CKD patients.

METHODS

An observational non control study has been held at hemodyalisis center of Bethesda Hospital and Panti Rapih Hospital, Yogyakarta, Indonesia. This study conducted from August to October 2018. The minimum subjects requirement in this study were 120 subjects. Each subject would be followed for 4 weeks.

Every male or female, age >18 years, diagnosed with CKD, and has a routine hemodyalisis two times per week with time interval between each hemodyalisis was 3 to 4 days was included. The sequence of hemodyalisis per week reffered as "first hemodyalisis" and "second hemodyalisis" in order to easy to describe. Subjects who did 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 would be excluded.

Every hemodyalisis subject in Bethesda Hospital and Panti Rapih Hospital has a routine intravenous injection of vitamin B combination, consist of 100 mg vitamin B_1, 100 mg vitamin B_6, and 5000 mcg vitamin B_{12}, after each hemodyalisis. Subject with a history of routine vitamin B combination supplementation was not allowed in this study. Each subject participating in this study have to signed an informed consent form.

Demographic data, medical history, co-treatment, fatigue scale, and the presence of adverse event were assessed in this study. Demographic data includes: age, gender, marital status, educational degree, and working status. Age classified into >70, 70-61, 60-51, 50-40, and <40 years. Marriage status differed into married and not married, which is including single and divorce. Educational degree classified into undereducated (unschooled or elementary school), high school (junior or senior high school), and diploma, bachelor's degree, or higher. Working status differentiated into working and unemployment.

VAS in this study has been used to measure the intensity of fatigue. A straight horizontal line of 10 cm was made, 0 at the left end reffered as "no fatigue at all" and 10 at the right end reffered as "complete exhaustion". Subjects asked to mark the line at the point that they feel represent their current fatigue state. The VAS score was determined by measuring in centimeters from the left end to the mark. The VAS score measured at visit I (before the first hemodyalisis), visit II (2 weeks after visit I, after the second hemodyalisis), and visit III (2 weeks after visit II, after the second hemodyalisis). The VAS score reduction would be test for normality using Kolmogorov-Smirnov and continued using paired t test or Wilcoxon test. Delta (Δ) VAS I – II and Δ VAS I – III defined as the shifting of VAS score from the first week to the second week and from the first week to fourth week. Other variables (age, gender, marital status, educational degree, and working status) were analyzed using Kruskal Wallis test or Mann Whitney U Test to identify other contributing factor(s) to VAS score reduction from first week to last week. The significant level was set at $p < 0.05$.

QoL measured using SF-8 questionnaire. The questionnaire contains 8 questions about daily physical and mental status. Each question has 5 or 6 answer choices which is scored 1 to 5 or 6 consecutively. Questions 1 to 5 consist of general health perception, physical functioning, physical role functioning, bodily pain, vitality. The final results will be summarized into physical component (PCS). Question 6 to 8 consist of social social role function, mental health, and emotional role functioning. The final results will be summarized into mental component (MCS). A higher score of PCS and MCS indicates a worse QoL. QoL measured at visit I and visit III.

Evaluation of adverse event in this study was done at the second and fourth week. Adverse event would be differed into: adverse event related to vitamin B combination and not related to vitamin B combination. Every adverse event would be recorded, reported, and handled according to management protocol in each study center. The severity of adverse event would be evaluated to determine the needed of hospitalization.

Ethical clearance process was done in Duta Wacana Christian University School of Medicine Ethical Research Committee. The number of ethical clearance 614/C.16/FK/2018. As this study used a primary data, informed consent process will be made very clearly. Each subject who refuse to be involved in this study are not required to explain their reason and will not affect their therapy. All data in this study will be classified and used only for research purposes.

RESULTS

Total of 122 subjects included in this study. Subjects dominated by male (63.9%) aged between 51-60 years (31.3%). Most subjects are married, well educated, and have an occupation. Anemia and hypertension were the common comorbidities in subjects.

Table 1. Characteristics of Subjects at Baseline

Characteristics	Number of Subjects (n=122)	%
Gender:		
Male	78	63.9
Female	44	36.1
Mean age	51.7 ± 12.6 years	
Age		
>70	25	20.5
61-70	25	20.5
51-60	38	31.3
40-50	31	25.4
<40	3	2.5
Marital status		
Married	101	82.8
Not married	21	17.2
Educational background		
Undereducated	12	9.8
High school	53	43.4
Diploma, bachelor degree or higher	57	46.7
Working history		
Working	96	78.7
Unemployment	26	21.3
Medical history:		
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

Degree of fatigue assessed using VAS. The prevalence of fatigue was high. At the baseline, 46.7% subjects has VAS score above mean VAS score (mean VAS score at baseline: 3.4 ± 2.1). Improvement on degree of fatigue was shown in this study after administration of intravenous vitamin B combination. The number of subjects who did not fatigue at all (indicate by VAS score 0) was increasing from the first to the last week : 3 subjects at the first week, 5 subjects at the second week, and 7 subjects at the last week. Mean VAS score was decrease gradually from the first week to the last week, as shown in table 2. The maximum VAS score was also decrease from the first week to the fourth week.

Table 2. VAS for Fatigue

Visit	Mean Score	Min Score	Max Score
Visit I	3.4	0	9.3
Visit II	2.9	0	10
Visit III	2.7	0	8.8

The prevalence of fatigue was decreasing, from 46.7% at baseline to 41% at the last week. Mean VAS score reduction was higher at ΔVAS I – III compared to ΔVAS I – II (Table 3). The degree of VAS score reduction (ΔVAS) was 64.4% from baseline to the second week and 62.4% from baseline to the fourth week. The reduction of VAS score from the first to the last week was statistically significant (p: 0.008).

Table 3. VAS Score Reduction

Visit	Mean Reduction Score	Percentage of Reduction Score	p
ΔVAS I – II	0.4 ± 1.9	64.4%	0.054
ΔVAS I – III	0.7 ± 2.3	62.4%	0.008

ΔVAS 1 – 2: the shifting of VAS score from the first week to the second week; ΔVAS 1 – 4: the shifting of VAS score from the first week to the fourth week

Further analysis on other variables were made to identify other factors influencing the presence of fatigue. Age, gender, marital status, working history, educational background, and medical history were not related to fatigue (Table 4).

Table 4. Analysis on Variables

Variables	Mean VAS Score	p
Gender		0.712
Male	3.4 ± 2.1	
Female	3.5 ± 2.1	
Age		0.503
>70	2.9 ± 0.3	
61-70	3.1 ± 2.2	
51-60	3.6 ± 2.1	
40-50	3.5 ± 2.3	
<40	3.6 ± 1.9	
Marital status		0.789
Married	3.3 ± 2.1	
Not married	3.8 ± 1.9	
Educational background		0.657
Undereducated	2.9 ± 1.9	
High school	3.3 ± 2.0	
Diploma, bachelor degree or higher	3.7 ± 2.2	
Working history		0.147
Working	3.4 ± 2.0	
Unemployment	3.2 ± 2.3	
Medical history		
Hypertension	3.5 ± 2.1	0.627
Diabetes mellitus	3.7 ± 2.2	0.346
Cardiovascular disease	3.9 ± 2.2	0.158
Stroke	3.8 ± 3.2	0.786
Congenital kidney disease	1.1 ± 1.1	0.119
Urinary tract calculus	3.0 ± 2.3	0.329
Anemia	3.4 ± 2.2	0.955
Dyslipidemia	3.5 ± 1.8	0.385
Urinary tract infection	2.3 ± 0.9	0.795

Figure 1 showed the mean score for total component, PCS, and MCS. The higher score represent a worse QoL. QoL was improved after 4 weeks of treatment indicated by a lower mean score at the visit III. Physical problems were more common than mental problems among subjects.

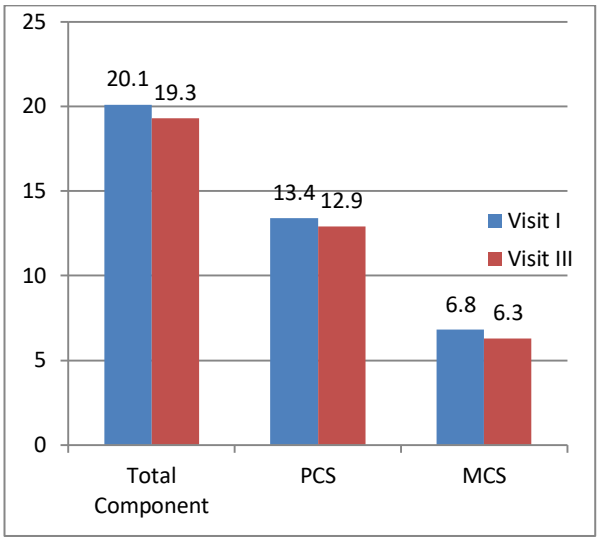

Figure 1. Mean Score of Quality of Life

After 4 weeks of treatment, there was a score reduction in total component, PCS, and MCS. Both PCS and MCS had a similar degree of score reduction (Table 5). This score reduction indicated an improvement of QoL. However, the score reduction was not statistically significant (Table 5).

Table 5. Quality of Life Score

QoL Component	Mean Score Visit I	Mean Score Visit III	Mean Reduction Score	p
Total component	20.19 ± 4.8	19.29 ± 4.9	0.89 ± 5.4	0.070
PCS	13.44 ± 3.1	12.99 ± 3.5	0.44 ± 3.6	0.181
MCS	6.75 ± 2.1	6.31 ± 1.9	0.44 ± 2.5	0.065

QoL: quality of life; PCS: physical components; MCS: mental components

After observation for 4 weeks, there was no adverse event related to administration of intravenous vitamin B combination. There were two subjects who had a complication during this study and it was observed at the visit II. One subject had a history of recurrent dyspneu and worsened during the study. This subject diagnosed with acute lung oedema, needed to be hospitalized, and the frequency of hemodyalisis changed to three times per week. The second subject died during the study due to metabolic complication. After a further investigation, there was no correlation between those complication with the administration of vitamin B combination.

DISCUSSION

VAS is a general instrument to measure the degree of symptom, in many conditions or diseases.[12-17] Some previous studies has already used VAS to measure the degree of fatigue.[12-14,17] This study was also using VAS as the instrument to measure the degree of fatigue.

The prevalence of fatigue is high as shown in this study. The mean VAS score was 3.4 ± 2.1 at baseline and there were 46.7% subjects with VAS score above the mean VAS score. The prevalence of fatigue is different in many previous researches due to the difference of treatment modality and measurement instrument used. This current study was using VAS to evaluate fatigue severity in CKD patients. VAS was chosen in this study due to its simplicity and easy to use in daily practice. It is only takes a short time to mark the line. Previous study in 508 hemodyalisis patients showed the prevalence of fatigue using VAS was 81.5%.[19] Fatigue measurement using fatigue assessment scale (FAS) on 129 hemodyalisis patients showed that 47.3% subjects were fatigue and 13.7% were extremely fatigue.[20] Excessive tiredness was the most common symptom (81%) in CKD patients stage I-V assessed using Leicester Uraemic Symptom Score.[21] Fatigue assessment on 47 hemodyalisis patients for 3 months using fatigue severity scale revealed the prevalence of fatigue was 44.7%.[22]

This present study showed fatigue was more common in female, age 51-60 years, not married, well educated, working, and had a history of cardiovascular disease. However, those variables were not associated with fatigue. This result is similar to previous researches. Study in 92 patients with ESRD showed no difference in level of fatigue between gender.[23] Cross sectional study of 87 non-dialysis dependent CKD and 86 ESRD patients showed there was no association of age, gender, and diabetes with fatigue.[1] Observational cohort study on 109 subjects, anemia was not associated with fatigue.[24] Research by Zyga, *et al*. (2015) also mention that marital status did not affect significantly any of the three fatigue indices in FAS.[20] No correlation between

employment and fatigue as stated by O'Sullivan, *et al*. (2007).[25]

Vitamin B combination used in this study contains 100 mg vitamin B_1, 100 mg vitamin B_6, and 5000 mcg vitamin B_{12}. After administration of vitamin B combination intravenously, the mean VAS score was decreasing from 3.4 at baseline to 2.7 at the last week and the prevalence of fatigue was decreasing, from 46.7% at baseline to 41% at the last week. This shifting is statistically significant (p: 0.008).

Vitamin deficiencies are common in advanced renal failure and hemodyalisis patients.[26,27] Patents with CKD have a risk for insufficient or deficient concentrations of vitamin B_1.[28] CKD patients at stage 3 or worse are at an increased risk for deficient concentrations of vitamin B_6.[18] A hospital based cross sectional study on 50 CKD patients showed a high prevalence of vitamin B_{12} deficiency in CKD patients.[29] Fatigue has been associated with vitamin B deficiency, especially vitamin B_{12} deficiency.[30] Based on literature review of 89 articles by Rusher and Pawlak (2013) shows fatigue is the common symptom cause by vitamin B_{12} deficiency.[31] Study by Tayyebi, *et al*. (2013) in 86 hemodialysis patients shows the effectiveness of vitamin B_{12} on the reduction of fatigue in hemodialysis patients.[32] They recommend administration of intravenous injection of 100 mcg/mL of vitamin B_{12} weekly after dialysis for hemodialysis patients. Research on 202 hemodyalisis patients conclude that nutritional supplementation, including vitamin B_1, vitamin B_6, vitamin B_{12}, may modulate immune and autonomic dysfunction in ESRD patients undergoing hemodialysis.[33] People with CKD regardless of whether they are predialysis or receiving either peritoneal or hemodialysis experience high levels of fatigue.[34]

Physical problems were more common among CKD patients than mental problems (Figure 1). This result was similar to previous studies by Cruz, *et al*. and Kefale, *et al*. QoL decreased in all stages of kidney disease. A reduction in physical functioning, physical role functioning, and in the PCS was observed progressively in the different stages of kidney disease.[35] Subject with CKD had reduction in several physical components (physical functioning [p: 0.03], bodily pain [p: 0.004], vitality [p: 0.019]) than mental component (social functioning [p: 0.002]).[36]

After 4 weeks of treatment, there was a score reduction in total component (20.19 ± 4.8 to 19.29 ± 4.9), PCS (13.44 ± 3.1 to 12.99 ± 3.5), and MCS (6.75 ± 2.1 to 6.31 ± 1.9). This score reduction indicated an improvement of QoL. The lower score indicated a better QoL. However, the score reduction was not statistically significant (total component: 0.070, PCS: 0.181, MCS: 0.065).

CONCLUSION

The prevalence of fatigue in this study is high. Administration of intravenous vitamin B combination two times per week after hemodyalisis proved to be effective and safe to reducing the degree of fatigue in CKD patients. The QoL in CKD patients was improved but not statistically significant.

CONFLICT OF INTEREST

There is nothing to declare.

AUTHORS' CONTRIBUTIONS

All authors had an equal contribution in this study.

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