The Effects of Early Vitamin B12 Replacement Therapy on The Cognitive and Functional Status of Elderly Subjects

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ÖZET:

Yaşlılarda erken vitamin B12 replasman tedavisinin kognitif ve fonksiyonel durumlara etkileri

Amaç: Bu çalışmanın amacı düşük vitamin B12 düzeyli yaşlılarda erken vitamin B12 replasmanının kognitif ve fonksiyonel durumlara etkilerini nöropsikolojik değerlendirme ölçekleri ile incelemektir.
Yöntem: Bu çalışmada düşük vitamin B12 düzeylerine (<400 pg/ml) sahip 116 kognitif bozukluğu olan hasta ve 211 kognitif bozukluğu olmayan toplam 327 yaşlı olgu değerlendirildi. Olgulara ilk bir ay haftada bir, daha sonra beş ay süreyle de ayda bir 1000 mikrogram intramusküler siyanokolbalamin verildi. Tüm hastalar başlangıçta ve 6 ay sonra mini-mental durum değerlendirmesi, saat çizme testi, günlük yaşam aktiviteleri ve enstrümantal günlük yaşam aktiviteleri ölçekleri ile değerlendirildi.
Bulgular: Altıncı aydaki değerlendirmede 120 olgu değişik nedenlerden dolayı vitamin B12 replasmanı almamıştı. Bu olguların tam kan parametreleri stabil kalırken, vitamin B12 düzeyleri, kognitif ve fonksiyonel ölçek skorları anlamlı olarak kötüleşmişti (p değerleri < 0.05). Bununla birlikte, vitamin B12 replasmanı almış 207 olgunun vitamin B12 düzeylerinde, mini-mental durum değerlendirmesi ve saat çizme ölçeklerinin skorlarında istatistiksel olarak anlamlı artma (p değerleri < 0.05) ve günlük yaşam aktivitesi ile enstrümantal günlük yaşam aktivitesi ölçeklerinin skorlarında korunma gösterdi.
Sonuç: Sonuç olarak, geriatrik olgularda vitamin B12 düzeylerinin yakın takibi, vitamin B12 düzeyleri 400 pg/ml den daha düşük olan hastalara erken replasman yapılması, kognitif durumun gelişmesi ve fonksiyonelliğin korunması açısından faydalı gibi görünmektedir.

Anahtar sözcükler: Vitamin B12, bilişsel işlev, fonksiyonel durum, yaşlı

Klinik Psikofarmakoloji Bülteni 2010;20:115-119

ABSTRACT:

The effects of early vitamin B12 replacement therapy on the cognitive and functional status of elderly subjects

Objective: The aim of this study was to examine the effects of early vitamin B12 replacement on cognitive and functional status in elderly subjects with low vitamin B12 levels by using neuropsychological assessment scales.
Methods: A total of 327 elderly patients with low vitamin B12 levels (<400 pg/ml) were evaluated. While 116 of 327 patients had cognitive impairment, 211 subjects did not. All patients were prescribed 1000 micrograms cyanocobalamin intramuscularly every week for 1 month, then monthly for 5 months. The mini-mental status examination (MMSE), clock drawing test, activities of daily living, and instrumental activities of daily living scales were applied to all patients at baseline and 6 month.
Results: At the 6-month evaluation it was found that 120 subjects have received only 1 dose or no vitamin B12 supplementation for various reasons. While their complete blood count parameters were stable; vitamin B12 levels, cognitive and functional scales' scores worsened significantly (p values <0.05). However, 207 subjects who had received 2 or more doses of B12 supplementation, showed statistically significant increase in their vitamin B12 levels, mini-mental state examination, clock drawing scales' scores (p values <0.05) and preservation in their activities of daily living and instrumental activities of daily living scales' scores.
Conclusion: Testing and close follow-up for vitamin B12 levels and early supplementation of vitamin B12 levels <400 pg/ml in geriatric subjects seem to improve the cognitive status and maintain the functional status.

Key words: Vitamin B12, cognitive function, functional status, elderly

Bulletin of Clinical Psychopharmacology 2010;20:115-119

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Kabul tarihi / *Date of acceptance:*
24 Mart 2010 / March 24, 2010

Bağıntı beyanı:
E.B., A.T.I., H.D., S.K.: yok.

Declaration of interest:
E.B., A.T.I., H.D., S.K.: none.

INTRODUCTION

Despite the fact that vitamin B12 deficiency is classified among the reversible causes of dementia (1), the association between vitamin B12 levels and the cognitive problems of elderly patients is still a topic of debate (2). Although some studies have found low levels of vitamin B12 in patients with dementia (3-6); it has also been reported that vitamin B12 deficiency was not a risk factor (7-9) and that vitamin B12 replacement did not impact the cognitive functions (10-12).

The studies which have found vitamin B12 replacement to be ineffective, the threshold level of vitamin B12 deficiency for treatment was taken as 150-200 pg/ml (10-12). Moreover, we are aware of only one study, which has found vitamin B12 supplementation in patients with vitamin B12 <300 pg/ml, was favorable (13). A study recommended that the lower limit of the

normal range for vitamin B12 level should be increased to 300 pg/ml (14).

On the other hand, according to the guidelines of American Family Physicians (2) vitamin B12 levels between 100 and 400 pg/ml is accepted to be borderline and should be further evaluated. To the best of our knowledge vitamin B 12 replacement in elderly patients with vitamin B12 levels less than 400 pg/ml has not been studied before. The aim of this study was to evaluate the early effects of vitamin B12 replacement on cognitive and functional performance of elderly subjects who had vitamin B12 levels < 400 pg/ml.

METHODS

The study was carried out at our outpatient geriatric clinic. All subjects gave informed consent to participate after standard information about study procedures. The study protocol was approved by Local Ethics Committee.

All patients (age ≥ 65 years) who were referred to our outpatient clinics were recruited. Demographic features and detailed medical history were noted. Systemic physical examination and a comprehensive geriatric evaluation were performed on each patient. Geriatric assessment tools comprised Mini-Mental State Examination (MMSE) (scored between 0-30), clock drawing test (CDT) (scored between 0-4), activities of daily living (ADL) (Barthel index) scored between 0-100), and instrumental activities of daily living (Lawton-Brody scale) (IADL) (15). Laboratory tests included complete blood count, erythrocyte sedimentation rate, liver/renal/thyroid function tests, vitamin B12 and folate levels, urinalysis, and fecal blood sampling. Those patients who were suspected to have cognitive dysfunction were further evaluated with cranial magnetic resonance imaging.

Eventually, subjects with vitamin B12 levels less than 400 pg/ml were enrolled in the study. Exclusion criteria were the presence of any of the followings: Iron deficiency anemia, positive fecal blood, folate deficiency, severe dementia, thyroid dysfunction, and chronic liver disease (cirrhosis).

Patients were then divided into two groups according to the presence of cognitive dysfunction. Parenteral vitamin B12 replacement was prescribed to all of the subjects (i.m. vitamin B12 5 doses weekly, then 5 doses monthly). After 6 months, the patients were re-evaluated thoroughly and were categorized into 4 groups according to their treatment compliance (Figure 1). Those subjects who had received at least 2 injections during the 6 month period were accepted as treatment positive, and those who had received one or no injection were accepted as treatment negative.

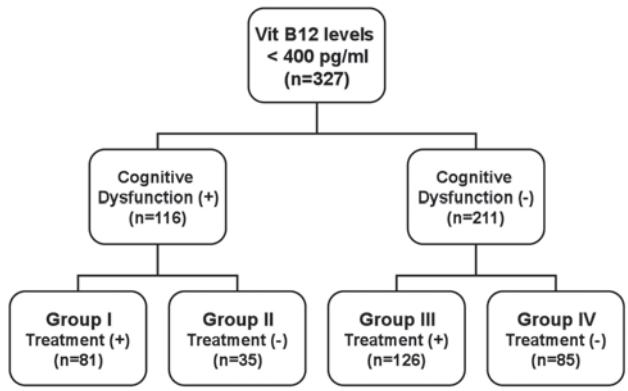

Figure 1: Categorization of the subjects according to cognitive status and treatment compliance

Statistical analyses were performed using SPSS software version 15.0 (Chicago IL, SPSS Inc). Demographics and baseline characteristics are reported as the number (n) and percentage (%) for nominal variables and as the mean ± SD for continuous variables. Levene's test was used to evaluate the equality of variance. Differences between the groups were tested for significance by independent samples t test, and paired t test, as appropriate. The relationship between variables was analyzed by Pearson's correlation. The differences and correlations were considered significant at $p<0.05$.

RESULTS

Overall, 568 patients who had vitamin B12 levels less than 400 pg/ml were recruited. Among those 351 subjects fulfilled the inclusion/exclusion criteria. During the study period, 24 patients were lost to follow up; and 327 patients (191 Male, 136 Female) completed the study. The study groups are shown in Figure 1.

Demographic features and laboratory test results of the subjects are summarized in Table 1. Hematological parameters, folate and thyroid stimulating hormone levels were similar between the groups (p values >0.05). Geriatric assessment results are given in Table 2. When

Table 1: Demographic features and baseline laboratory test results (*) of the subjects

	Group 1 (n=81)	Group 2 (n=35)	Group 3 (n=126)	Group 4 (n=85)
Age (year)	77.2±5.1	78.7±4.9	74.7±5.5	75.8±5.8
Sex (M/F)	35 / 46	16 / 19	50 / 76	35 / 50
Education (year)	6.52±4.27	6.97±3.88	7.40±4.34	7.81±4.19
Hgb (mg/dl)	13.5±1.5	13.7±1.6	13.6±1.4	13.8±1.5
Hct (%)	40.0±4.3	40.7±4.5	40.4±4.0	40.7±4.1
MCV (fl)	88.8±5.6	88.5±5.4	89.1±6.8	89.2±4.5
Vitamin B12 (mg/dl)	264.5±81.6	326.1±119.4	260.4±78.0	341.8±126.1
Folate (mg/dl)	9.53±3.99	9.37±3.92	9.27±3.15	9.89±3.17
TSH (µIU/ml)	1.94±1.27	2.18±1.42	1.71±0.98	1.89±1.11

*: Mean ± SD. Hgb: Hemoglobin, Hct: Hemotocrit, MCV: Mean corpuscular volume, TSH: Thyroid stimulating hormone.

Table 2: Baseline geriatric assessment results (*) of the subjects

	Group 1 (n=81)	Group 2 (n=35)	Group 3 (n=126)	Group 4 (n=85)
MMSE	20,81±5,60	23,97±4,29	27,61±2,06	28,45±1,91
CDT †	2,65±1,23	3,00±0,93	3,76±0,56	3,76±0,46
ADL	90,1±15,6	95,7±9,4	97,3±5,6	96,4±5,3
IADL	11,08±5,52	12,74±4,47	15,24±2,81	15,25±3,67

* : Mean ± SD, † : (applied to subjects (N=65, 30, 111, 74, respectively) with ? 5 years of education), MMSE: Mini-mental state examination (Folstein, scored 30 points), CDT: Clock drawing test (scored 4 points), ADL: Activitaminies of daily living (Barthel Index, scored 100 points), IADL: Instrumental activitaminies of daily living (Lowton-Brody, scored 17 points).

Table 3: Comparisons between pre- and post-treatment values (*) of the subjects

	Group I			Group II			Group III			Group IV		
	Pre	Post	p †	Pre	Post	p †	Pre	Post	p †	Pre	Post	p †
Hgb (mg/dl)	13,5±1,5	13,6±1,3	,532	13,7±1,6	13,9±1,4	,431	13,6±1,4	13,8±1,5	,193	13,8±1,5	13,5±1,6	,061
Hct (%)	40,0± 4,3	40,1± 3,9	,853	40,7±4,5	40,8±3,9	,610	40,4±4,0	40,4±4,0	,987	40,7±4,1	39,9±4,5	,082
MCV (fl)	88,8± 5,6	88,4± 4,9	,441	88,5±5,4	87,9±4,5	,423	89,1±6,8	88,3±4,9	,159	89,2±4,5	89,2±4,6	,989
Vit B12 (mg/dl)	265.1±82.2	725±443	,000	326±119	268±71	,001	260±78	637±332	,000	342±126	279±61	,000
MMSE	20,8±5,6	22,6±5,4	,000	24,0±4,3	21,6±5,4	,000	27,6±2,1	28,8±1,7	,000	28,5±1,9	26,8±2,7	,000
CDT ‡	2,65±1,23	3,03±1,13	,008	3,00±0,93	2,80±1,16	,161	3,76±0,56	3,85±0,45	,032	3,76±0,46	3,51±0,62	,000
ADL	90,1±15,6	90,3±13,9	,278	95,7±9,4	90,9±12,3	,007	97,3±5,6	96,4±6,5	,073	96,4±5,3	94,6±7,9	,033
IADL	11,1±5,5	10,8±5,3	,255	12,7±4,5	11,3±5,5	,001	15,2±2,8	15,4±2,8	,151	15,6±3,7	14,3±4,3	,001

* : Mean ± SD, † : Paired sample t test, ‡ : (applied to subjects (n=65, 30, 111, 74, respectively) with ? 5 years of education), Hgb: Hemoglobin, Hct: Hemotocrit, MCV: Mean corpuscular volume, MMSE: Mini-mental state examination (Folstein, scored 30 points), CDT: Clock drawing test (scored 4 points), ADL: Activities of daily living (Barthell Index, scored 100 points), IADL: Instrumental activities of daily living (Lowton-Brody, scored 17 points),

subjects were compared according to their cognitive status; those with cognitive dysfunction were found to be older ($p<0.05$), and they had worse scores in MMSE, CDT, ADL and IADL tests (p values <0.01). When patients were compared according to their compliance to vitamin B12 replacement, vitamin B12 levels and cognitive assessment scores were found to be lower in those subjects who complied with treatment (p values <0.05).

Comparisons between the pre- and post-treatment evaluations are given in Table 3. Regarding the laboratory and geriatric assessment results of the subjects; in non-compliant patients, although hematological parameters were found to be similar, vitamin B12 levels and geriatric assessment scales' results worsened significantly based on baseline and repeat tests. On the other hand, in patients compliant with the treatment, hematological parameters were again similar; however vitamin B12 levels and cognitive performance improved significantly and functional performance preserved at 6 month repeat tests.

DISCUSSION

In this study, we evaluated the early effects of vitamin B12 replacement therapy on cognitive and functional performance of elderly subjects, who had vitamin B12 levels less than 400pg/ml. According to our results, the failure to replace vitamin B12 effected the cognitive and functional performance unfavorably and vitamin 12 treatments improved the cognitive performance and maintained the functional performance in the six months follow up.

In the elderly population, it is known that neurological dysfunction due to vitamin B12 deficiency may well ensue before the onset of hematological problems (16). Likewise, in our study, despite all of the subjects had normal hematological parameters, some already had cognitive problems. Furthermore, both cognitive and functional deterioration occurred in those subjects who did not receive vitamin B12 replacement.

It has been previously reported in several studies that serum vitamin B12 levels and cognitive function is inversely related (3,17) and that vitamin B12 deficiency is a risk factor for the development of dementia (5,6). This is true not only for vascular dementia (18) but also for Alzheimer's disease (4,19). Similarly, our results have shown that in patients who did not receive vitamin B12 replacement whether they have cognitive dysfunction or not, serum levels of vitamin B12 decreased along with cognitive and functional performance. Despite the fact that 200 pg/ml is generally accepted as the value for absolute vitamin B12 deficiency, in order to encompass subjects with mild deficiency, we have also included those with vitamin B12 levels of less than 400 pg/ml in our study.

In a retrospective study of Eastley et al., vitamin B12 replacement was found not to have improved cognitive functions (11). In here, mean vitamin B12 levels of patients who had received treatment was 142 pg/ml and mean MMSE score was 17.2. On the other hand, it is known that various irreversible changes were reported at this level (2,20,21). In our study, mean vitamin B12 level was 283 pg/ml and mean MMSE score was 21,8 in subjects with cognitive dysfunction. Moreover, our results demonstrated that patients have benefited from early replacement therapy.

Bronx Longitudinal Aging Study compared the prevalence rates of dementia among subjects with vitamin B12 levels below and above 150 pg/ml and they have reported that vitamin B12 deficiency was not a risk factor for dementia (7). However, if they had accepted the threshold level higher, they might have found an association between low vitamin B12 levels and dementia. Likewise, we have taken subjects with vitamin B12 levels below 400 pg/ml as vitamin B12 deficient and treated them accordingly.

In another study, vitamin B12 replacement therapy was found to be ineffective after 3 months both with regard to hematological or neuropsychiatric parameters; whereas subgroup analysis for subjects with and without cognitive dysfunction or concerning geriatric patients was not performed (12). Similarly, Teunisse et al (10) have reported that a 6-month parenteral replacement therapy for subjects with vitamin B12 levels below 200 pg/ml did not decrease the progression of dementia. In contrast our findings imply that early replacement therapy for vitamin B12 <400 pg/ml before vitamin B12 levels decrease to levels reported in those studies would be effective based on 6-month follow up findings. Furthermore, we have shown that vitamin B12 replacement had beneficial effects on the activities of daily living, as well. Yet, although patients who received vitamin B12 maintained their functional status, the ones, who did not receive treatment, had worsened functional status.

Based on our results, we conclude that early vitamin B12 replacement (for subjects with vitamin B12 levels <400 pg/ml) has favorable effects on the cognitive function and it helps to maintain the functional status. Therefore, we suggest that replacement and close follow up of vitamin B12 deficiency are crucial in the elderly population regardless of any disturbance in the hematological parameters.

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