International Journal of Contemporary Pediatrics
Sarbay H et al. Int J Contemp Pediatr. 2022 May;9(5):412-417
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20221064

Original Research Article

Comparison of the low-dose oral therapy results with literature and parenteral therapy in children with vitamin B12 deficiency

Hakan Sarbay[1]*, Mehmet Akin[2]

[1]Department of Pediatric Hematology and Oncology, Faculty of Medicine, TC Istanbul Yeni Yuzyil University, Istanbul, Turkey
[2]Department of Pediatric Hematology, Goztepe Medical Park Hospital, Istanbul, Turkey

Received: 22 December 2021
Revised: 31 January 2022
Accepted: 15 March 2022

***Correspondence:**
Dr. Hakan Sarbay,
E-mail: drhakansarbay@hotmail.com

ABSTRACT

Background: It was aimed to investigate the results of vitamin B12 deficiency treatment with a lower vitamin B12 loading dose and compare with literature.
Methods: Patients diagnosed with vitamin B12 deficiency at the pediatric hematology and oncology clinic between May 2017 and May 2018 were evaluated retrospectively. Patients who received a total of five doses of oral or parenteral cyanocobalamin treatment, 500 mcg two days a week in terms of region's socio-cultural status and accessibility to the health institution were included in the study. Vitamin B12 deficiency was defined as below 200 pg/ml. Post-treatment blood counts and vitamin B12 levels were reevaluated one month later after treatment was started. Vitamin B12 treatment responses were compared between the oral and parenteral groups and the results in the literature.
Results: Parenteral cyanocobalamin was used in 134 patients and oral cyanocobalamin was used in 146 patients. Post-treatment vitamin B12 values at first month were investigated in 115 and 123 children in parenteral and oral arms, respectively. A total of 238 patients were included in the study. Although control mean±standard deviation (SD) vitamin B12 values increased significantly in both groups. Compared to the literature, vitamin B12 mean±SD values (oral treatment group 349.48±179.12, parenteral treatment group 486.77±52.77) after treatment did not differ significantly according to higher doses and longer treatment.
Conclusions: In vitamin B12 deficiency, 500 mcg twice a week and a total of five dose oral cyanocobalamin is sufficient to increase the levels of vitamin B12.

Keywords: Vitamin B12 deficiency, Oral cyanocobalamin, Nutritional deficiency

INTRODUCTION

Vitamin B12 deficiency is an important health problem in developing countries and socio-economic low communities. The most common causes are maternal deficiency in infants who are breastfed and poor nutrition from animal food in childhood. Pernicious anemia, malabsorption disorders, vitamin B12 absorption disorders, transport disorders are other factors that cause vitamin B12 deficiency.[1] Vitamin B12 deficiency is the most common cause of megaloblastic anemia in childhood. Bicytopenia or pancytopenia can also be seen with the effect of other cell series besides anemia. Vitamin B12 is also important in terms of neurodevelopmental process with nervous system myelinization, besides cellular development. Irritability, weakness, hypotonia, ataxia, apathy, tremor, convulsion can be seen in severe deficiency. It is important to consider, diagnose and treat vitamin B12 deficiency in childhood. Although the treatment is simple and low cost, delay in treatment can cause serious complications such as severe anemia and neurological damage.[2,3] Vitamin B12 deficiency is

traditionally treated with parenteral treatment. In addition to this high dose of oral vitamin B12 has been used effectively for the treatment of vitamin B12 deficiency even in patients with pernicious anemia. In recent years, different forms of oral and parenteral treatment have been published in studies in adult patients.[4-6] In this study, the response to a lower vitamin B12 loading dose compared to the literature was investigated retrospectively and it was aimed to indicate the results.

METHODS

This was a non-randomized controlled retrospective clinical study. Patients diagnosed with vitamin B12 deficiency in Diyarbakir Children Hospital at the pediatric hematology and oncology clinic between May 2017 to May 2018 were evaluated retrospectively. Patients who received a total of five doses of 500 mcg oral or parenteral cyanocobalamin therapy for two days a week in terms of region's socio-cultural status and accessibility to the health institution were included in the study. Vitamin B12 deficiency was defined levels as less than 200 pg/ml. Detailed nutritional history and physical examination; complete blood count, peripheral smear, serum vitamin B12, folic acid, iron, iron binding capacity, ferritin levels were evaluated. Additional hematological diagnoses such as iron deficiency, hemoglobinopathy, folate deficiency, if any, were investigated by evaluating peripheral smear, folate, iron, iron binding capacity, ferritin levels and hemoglobin electrophoresis. Patients' age, gender, leukocyte (WBC), neutrophil (neut), platelet (Plt) counts, mean corpusculer volume (MCV), hemoglobin (Hgb), vitamin B12 pre-treatment and post-treatment levels mean and standard deviation (SD) values were calculated. The hemoglobin value below -2 SD according to age was defined as anemia. Leukocyte count below 4000 /mm^3 was regarded as leukopenia, neutrophil count below 1500 /mm^3 as neutropenia (<1000 /mm^3 below 1 year old age) and thrombocyte count below 150,000 /mm^3 as thrombocytopenia. Iron and folate deficiency was considered with ferritin and folate levels under 12 mcg/l and 5 ng/ml, respectively. Patients with iron and folate deficiency were given 5 mg/kg/day elementary iron treatment and folic acid 5 mg/day. Potassium level control was recommended on the 2nd day of the first treatment dose in all patients.

Post-treatment blood counts and vitamin B12 levels was controlled one month later after treatment was started. Vitamin B12 levels were measured in plasma. Samples were collected in the fasting state. Vitamin B12 levels were measured using chemiluminescence method by ARCHITECT i2000SR immunoassay analyzer (Abbott Park, Illinois, USA). In terms of response to the treatment, the control blood counts, the rate of the patients not responding to the treatment and the status of the neurological findings were evaluated. Failure to treat was defined as detecting control vitamin B12 level below 200 pg/ml. Vitamin B12 treatment responses were compared between the oral and parenteral groups and the results in the literature.

Methylmalonic acid, homocysteine, holotranscobalamin levels could not be investigated for the diagnoses because there were not adequate facilities. Patients who had additional hematological disease that may cause bicytopenia-pancytopenia and, patients that used different dose and duration vitamin B12 treatment were not included in the study. And also, 42 patients whose control vitamin B12 levels could not be evaluated one month after the initiation of treatment were excluded from the study.

This retrospective study was approved by local ethics committee in 8 March 2019 (2019-236). Approval statement for participation received from the legal authorized representatives of the participants.

Statistical analysis

The normality of distribution of continuous variables was tested by Shaphiro Wilk test. Mann-Whitney U test (for abnormal data) was used for comparison of two independent groups and Wilcoxon test was performed for comparison of dependent abnormal measurements. Chi square test was used to assess relation between categorical variables. Meta-analytic approach was applied to compare the study results with previously published studies. Forest plot graph was used to visually compare standardised mean difference (SMD) of studies.

Univariate statistical analysis was performed with statistical package for the social sciences (SPSS) for Windows version 24.0 and Medcalc package version 18.10.2 was used for Forest plot graph. A p value <0.05 was accepted as statistically significant.

RESULTS

Parenteral cyanocobalamin was used in 134 patients and oral cyanocobalamin was used in 146 patients. Patients' age, gender, WBC, neut, lymp, plt counts, MCV, Hgb, vitamin B12 levels mean and SD were evaluated (Table 1). Leukopenia in 5 patients (1%), neutropenia in 24 patients (8%), anemia in 117 patients (41%), thrombocytopenia in 23 patients (8%), macrocytosis in 49 patients (17%), bicytopenia in 18 patients (6%), pancytopenia in 9 patients (3%) was detected. Of the 280 patients whom vitamin B12 treatment was started, 112 (40%) had iron deficiency, 25 (8%) had thalassemia minor and 3 (1%) had sickle cell disease. Three of the 280 patients (1%) had celiac disease and these patients were in the parenteral treatment group. In the physical examination of the patients, neurological findings were detected in 15 patients (5%).

These findings included delayed neuromuscular development, headache, coordination disorders, muscle weakness, parasthesis in the hands. When patient records were evaluated, neurological findings were observed in only one patient in both groups during the controls one

month after the start of treatment. Bicytopenia, pancytopenia, leukopenia and thrombocytopenia were not detected, in addition to these, only one patient in both groups had mild neutropenia in the first month control blood counts of patients who have pre-treatment cytopenia.

Post-treatment vitamin B12 values at first month were investigated in 115 and 123 children in parenteral and oral treatment groups, respectively. Control mean±SD vitamin B12 values increased significantly in both groups. There was no significant difference between the two groups in terms of the proportion of patients whose vitamin B12 level reached normal limits (Tables 2 and 3).

Compared to the literature, vitamin B12 mean±SD values after treatment did not differ significantly according to higher doses and longer treatment (Tables 4 and 5) (Figures 1 and 2).

Table 1: General characteristics and laboratory values of the patients.

Variables (n=280)	Descriptive statistics (mean±SD)	
Age	5.21±5.67	
Vitamin B12	136.50±32.68	
Hemoglobin	11.05±11.20	
MCV	73.29±13.82	
WBC	9419.86±3688.91	
Neutrophil	3701.02±2112.32	
Platelet	358639.29±1692037.42	
Control vitamin B12	415.82±384.78	
	Count	%
Boy	166	59.3
Girl	114	40.7
Oral	146	52.1
Parenteral	134	47.9

Table 2: Comparison of oral and parenteral groups in terms of age and blood count parameters.

Variables	Oral (n=123)		Parental (n=115)		
	Mean±SD	Median (25-75%)	Mean±SD	Median (25-75%)	P value
Age	5.07±5.62	1.5 (1-9)	5.37±5.74	1 (1-11)	0.912
Hemoglobin	11.89±15.3	10.65 (8.9-12.5)	10.12±2.46	10.15 (7.9-12.1)	0.086
MCV	73.22±14.04	74.5 (61-83)	73.37±13.63	73.5 (63-84)	0.911
Leukocyte	9506.51±3724.19	8600 (6590-11920)	9325.45±3661.69	8970 (6850-11340)	0.904
Neutrophil	3771±2233.76	3395 (2140-4940)	3624.78±1977.08	3250 (2390-4760)	0.810
Platelet	373602.74±177910.42	346500 (265000-450000)	342335.82±141623.08	338500 (250000-419000)	0.226

*Significant at 0.05 level; Mann Whitney U test

Table 3: Comparison of vitamin B12 measurements within and between groups.

Variables	Oral (n=123)		Parental (n=115)		
	Mean±SD	Median (25-75%)	Mean±SD	Median (25-75%)	P value
Vitamin B12	145.82±32.94	155.5 (123-173)	126.34±29.28	127.5 (101-148)	0.001*
Control vitamin B12	349.48±179.12	299 (242-406)	486.77±352.77	390 (292-523)	0.001*
	0.001*		0.001*		
Difference	204.73±180.86	174 (107-258)	361.57±361.28	261 (170-403)	0.001*

*Significant at 0.05 level; Mann Whitney U test for between groups, Wilcoxon test for within group comparisons

Table 4: Comparison of oral treatment results with the literature.

Variables	Results	Sezer et al	Bahadır et al (4 months treatment)	Bahadır et al (8 months treatment)
Pre-treatment vitamin B12 levels (mean±SD)	145.82±32.94	183.5±47	158.4±28.8	150.8±22
Post-treatment vitamin B12 levels (mean±SD)	349.48±179.12	482±318.9	414.9±277.9	331.2±181.5
	Total sample size	SMD	95% CI	
Results	269	-1,645	-1,923 to -1,367	
Sezer, 2018	135	-1,464	-1,853 to -1,075	
Bahadır, 2014 (4 months treatment)	30	-1,263	-2,064 to -0,462	

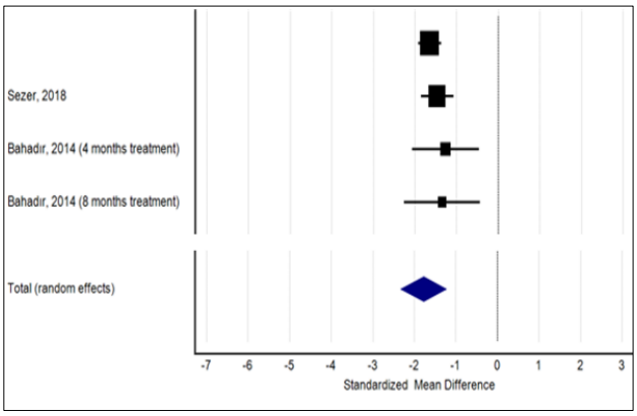

Figure 1: Comparison of oral treatment results with the literature.

Table 5: Comparison of parenteral treatment results with the literature.

Variables	Results		Sezer et al
Pre-treatment vit-B12 levels (mean±SD)	126.34±29.28		175.5±42.5
Post-treatment vit-B12 levels (mean±SD)	486.77±352.77		838±547
Study	Total sample size	SMD	95% CI
Results	249	-1.493	-1.776 to -1.211
Sezer, 2018	114	-1.743	-2.177 to -1.309

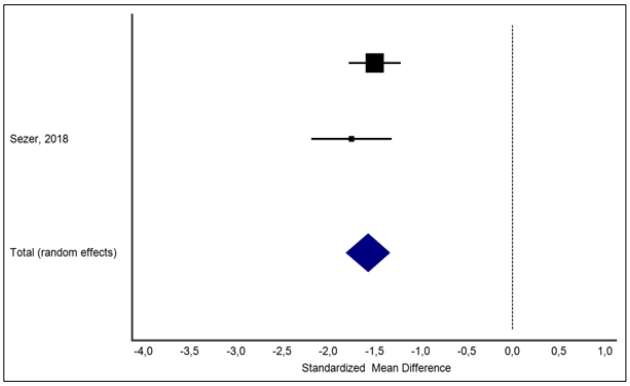

Figure 2: Comparison of parenteral treatment results with the literature.

DISCUSSION

Vitamin B12 has an important role in DNA synthesis; its deficiency caused megaloblastic anemia and serious problems such as neuromotor and developmental retardation. The daily requirement for vitamin-B12 was 1-2 µg/day. The dietary vitamin B12 disintegrated by the effect of gastric acid in the stomach and bonds to the intrinsic factor (IF) in the duodenum. The vitamin B12-IF complex is resistant to digestion, and it is absorbed by endocytosis in the terminal ileum. Only 1-2% of vitamin B12 can be absorbed independent of IF. Vitamin B12-IF complex is broken down after being taken into the cell and vitamin B12 binds to transcobalamin II and goes into enteral circulation.[7,8] Despite this complex journey of vitamin B12, vitamin B12 deficiency, which develops due to the deficiency of carrier proteins and IF, is very rare in children. It was thought that the main cause of deficiency was the inadequate vitamin B12 intake in the diet.[1,9] In our study, the diagnosis of pernicious anemia was not considered in our patients. A patient with proteinuria was diagnosed with Imerslund-Grasbeck disease. This patient was not included in the study because high-dose parenteral therapy was initiated. Three of the patients were diagnosed with celiac disease.

Vitamin B12 deficiency is classically treated with parenteral therapy. And the most common treatment is the intramusculer cyanocobalamine injections. Patients with deficiencies received injections of 1000 µg at least several times per week for 1 to 2 weeks, then weekly, followed by monthly injections.[10] Intramuscular injections were uncomfortable in children and also painful and prone to complications.[4] In a study in children, following an oral vitamin B12 therapy of 250 µg/day, serum vitamin B12 levels between 235 and 506 pg/dl were observed in 4 month follow-up.[11] Another study reported that orally administered 2 mg cyanocobalamin on a daily basis may be as effective as 1 mg cyanocobalamin administered intramuscularly on a monthly basis.[8] Oral treatment of vitamin B12 deficiency was also important for the children who cannot reach the hospital easily for parenteral administration of vitamin B12. The patient group who could not reach the health institution easily was the biggest reason for the emergence of this study.

The Turkish society of hematology recommended guidelines about oral vitamin B12 treatment for cobalamin deficiency. Intravenous ampules were mostly used, available form that contain solely vitamin B12 in Turkey. Oral tablets containing vitamin B12 consisted of other vitamins and elements. Ampules were suggested at a dosage of 250 to 1000 mcg/d for 1 week, then 2 days/week for 2 weeks, 1 day/week for 1 to 2 weeks, followed with monthly treatment until the levels normalized.

In a study conducted in our country, Sezer et al used parenteral cyanocobalamin as follows 100 mcg every day for 1 week, then 1000 mcg on alternate days for a week, then 1000 mcg two times a week for a week and finally once a week. In oral group a combination of multivitamin complex consisting of 50 mg thiamin, 250 mg pyridoxin and 1000 mcg cyanocobalamin one tablet was used per day up to one month. Both oral and parenteral formulations are found to be effective in normalizing vitamin B12 levels in children with nutritional vitamin B12 deficiency.[12] In a study using oral cyanocobalamin, children with vitamin

B12 deficiency were divided into groups according to age and duration of treatment. This study reported that oral vitamin B12 (1000 µg) for 4 months was effective for treatment of children with nutritional vitamin B12 deficiency. However, there was age related decline in vitamin B12 levels although not statistically significant results in this study.[13] In our study; while the increase in vitamin B12 levels was higher in the parenteral group, there was no difference in terms of normalization of vitamin B12 levels, improvement of neurological findings and cytopenias compared to the oral group. Compared to studies of Sezer et al and Bahadir et al, vitamin B12 values after treatment did not differ significantly according to higher doses and longer treatment.

In clinical and laboratory examination of vitamin B12 deficiency, different findings can be detected range from mild anemia to pancytopenia and from asymptomatic to severe neurological findings.[1] In a study, vitamin B12 deficiency was reported as the second most common cause of bicytopenia and pancytopenia infections.[14] Anemia was detected in 117 patients (41%), while bicytopenia was present in 18 patients (6%), and pancytopenia was present in 9 patients (3%). MCV may not always be a guide in the diagnosis of megaloblastic anemia. Especially in cases with iron deficiency, MCV may be within normal limits or low. Lindenbaum et al reported that MCV values were within normal limits in 28% of 141 children with B12 deficiency.[15] In this study, macrocytosis was detected in only 49 patients (17%). The reason for the low rate of macrocytosis compared to the literature was attributed to iron deficiency in 112 (40%) and thalassemia minor in 25 (8%).

As a result of the treatment of vitamin B12 deficiency, thrombocytopenia, neutropenia and leukopenia improve within 2-4 weeks.[16] Mild neutropenia persisted in only two of the patients with cytopenia at the time of initial diagnosis in control blood counts. One of the limitations of this study was the increase in hemoglobin levels could not be evaluated clearly because of high percentage of iron deficiency and thalassemia minor. The other was not able to reach adequate data about maintenance therapy due to follow-up discrepancy. After the start of treatment, the treatment response is important and can be stimulating for reasons other than nutritional deficiencies. However, in addition to the first month of treatment, maintenance therapy should be continued.

CONCLUSION

In conclusion, vitamin B12 deficiency is a common problem in children, proper and practical treatment is important for public health. Nowadays, vitamin B12 deficiency is a public health problem, especially in a period of intense regional wars and related migrations. 500 mcg twice a week and a total of five dose oral cyanocobalamin is sufficient to increase the levels of vitamin B12 in children who cannot reach the health institution easily and in socioeconomically low societies.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Stabler SP, Allen RH. Vitamin B12 deficiency as a worldwide problem. Annu Rev Nutr. 2004;24:299-326.
2. Honzik T, Adamovicova M, Smolka V, Magner M, Hruba E, Zeman J. Clinical presentation and metabolic consequences in 40 breastfed infants with nutritional vitamin B12 deficiency: what have we learned? Eur J Paediatr Neurol. 2010;14:488-95.
3. Strand TA, Taneja S, Ueland PM, Refsum H, Bahl R, Schneede J, et al. Cobalamin and folate status predicts mental development scores in North Indian children 12-18 mo of age. Am J Clin Nutr. 2013;97(2):310-7.
4. Wang H, Li L, Qin LL, Song Y, Vidal-Alaball J, Liu TH. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database Syst Rev. 2018;3(3):CD004655.
5. Bolaman Z, Kadikoylu G, Yukselen V, Yavasoglu I, Barutca S, Senturk T. Oral versus intramuscular cobalamin treatment in megaloblastic anemia: a single-center, prospective, randomized, open-label study. Clin Ther. 2003;25:3124-34.
6. Castelli MC, Friedman K, Sherry J, Brazzillo K, Genoble L, Bhargava P, et al. Comparing the efficacy and tolerability of a new daily oral vitamin B12 formulation and intermittent intramuscular vitamin B12 in normalizing low cobalamin levels: a randomized, open-label, parallel-group study. Clin Ther. 2011;33(3):358-71.
7. Sanz-Cuesta T, González-Escobar P, Riesgo-Fuertes R, Garrido-Elustondo S, del Cura-González I, Martín-Fernández J, et al. Oral versus intramuscular administration of vitamin B12 for the treatment of patients with vitamin B12 deficiency: a pragmatic, randomised, multicentre, non-inferiority clinical trial undertaken in the primary healthcare setting (Project OB12). BMC Public Health. 2012;12:394.
8. Kuzminski AM, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J. Effective treatment of cobalamin deficiency with oral cobalamin. Blood. 1998;92:1191-8.
9. Roschitz B, Plecko B, Huemer M. Nutritional infantile vitamin B12 deficiency: pathobiochemical considerations in seven patients. Arch Dis Child Fetal Neonatal Ed. 2005;90:281-2.
10. Oh R, Brown DL. Vitamin B12 deficiency. Am Fam Physician. 2003;67:979-86.
11. Vanderbrink BA, Cain MP, King S, Meldrum K, Kaefer M, Misseri R, et al. Is oral vitamin B12 therapy effective for vitamin B12 deficiency in patients with prior ileocytoplasty? J Urol. 2010;184:1781-5.

12. Sezer RG, Akoğlu HA, Bozaykut A, Özdemir GN. Comparison of the efficacy of parenteral and oral treatment for nutritional vitamin B12 deficiency in children. Hematology. 2018;23(9):653-7.
13. Bahadir A, Reis PG, Erduran E. Oral vitamin B12 treatment is effective for children with nutritional vitamin B12 deficiency. J Paediatr Child Health. 2014;50(9):721-5.
14. Sarbay H. Comparison of the severity of cytopenias with etiologic factors in patients with pancytopena and bicytopenia. Pan Afr Med J. 2019;34:149.
15. Lindenbaum J, Healton EB, Savage DG. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med. 1988;318:1720-8.
16. Whitehead VM, Rosenblatt DS, Cooper BA. Megaloblastic anemia. Hematology of Infancy and Childhood. In: Nathan DG, Oski FA, editors. Pediatrics haemotology. 6th edition. WB Saunders, Philadelphia. 2003;419-55.

Cite this article as: Sarbay H, Akin M. Comparison of the low-dose oral therapy results with literature and parenteral therapy in children with vitamin B12 deficiency. Int J Contemp Pediatr 2022;9:412-7.