DOI: 10.4274/gulhane.galenos.2024.47135
Gulhane Med J 2024;66(3):128-132

Comparison of the effectiveness of an oral combination of thiamine, pyridoxine, and cyanocobalamin with parenteral cyanocobalamin in adolescents with nutritional vitamin B12 deficiency

Ömer Güneş[1], Mehmet Ağıllı[2], Fatih Üçkardeş[3], Yüksel Hakan Aydoğmuş[1], Bahar Öztelcan Gündüz[1], Erman Ataş[4]

[1]University of Health Sciences Türkiye, Gülhane Training ve Research Hospital, Clinic of Pediatrics, Ankara, Türkiye
[2]University of Health Sciences Türkiye, Gülhane Training ve Research Hospital, Clinic of Medical Biochemistry, Ankara, Türkiye
[3]Adıyaman University Faculty of Medicine, Department of Biostatistics and Medical Informatics, Adıyaman, Türkiye
[4]University of Health Sciences Türkiye, Gülhane Training ve Research Hospital, Clinic of Pediatric Hematology-Oncology, Ankara, Türkiye

Cite this article as: Güneş Ö, Ağıllı M, Üçkardeş F, Aydoğmuş YH, Öztelcan Gündüz B, Ataş E. Comparison of the effectiveness of an oral combination of thiamine, pyridoxine, and cyanocobalamin with parenteral cyanocobalamin in adolescents with nutritional vitamin B12 deficiency. Gulhane Med J. 2024;66(3):128-132

Date submitted:
06.10.2023
Date accepted:
14.04.2024
Online publication date:
03.09.2024

Corresponding Author:
Ömer Güneş, M.D., Ankara Etlik City Hospital, Clinic of Pediatric Infectious Diseases, Ankara, Turkey
+90 312 552 60 00
dromergunes@gmail.com

ORCID:
orcid.org/0000-0001-7121-3810

Keywords: Vitamin B12, deficiency, adolescent, cyanocobalamin, treatment

ABSTRACT

Aims: Nutritional vitamin B12 deficiency remains a significant public health issue. This study aimed to compare the efficacy of an oral combination of thiamine, pyridoxine, cyanocobalamin, and parenteral cyanocobalamin treatment among adolescents with nutritional vitamin B12 deficiency.

Methods: This retrospective study included patients aged 12-18 years who applied to University of Health Sciences Türkiye, Gülhane Training and Research Hospital General Pediatrics Polyclinic between 2018 and 2019, and serum vitamin B12 levels were measured before and after parenteral or oral combination of thiamine, pyridoxine, and cyanocobalamin treatment.

Results: Of the subjects with post-treatment serum vitamin B12 levels above the target level of 200 pg/mL, parenteral cyanocobalamin was given to 34 patients with a median age of 16 years [interquartile range (IQR), 14 to 16 years], and girls (52.9%), and oral cyanocobalamin was given to 51 patients with a median age of 15 years (IQR, 13 to 16 years), and girls (58.8%). The mean serum vitamin B12 levels before parenteral and oral cyanocobalamin treatment were 150.32±6.49 pg/mL parenteral and 132.35±4.67 pg/mL in oral replacement groups ($p>0.05$). The mean serum vitamin B12 levels after parenteral and oral cyanocobalamin treatments were 566.0±62.77 pg/mL and 463.1±36.97 pg/mL, respectively ($p>0.05$). Both parenteral and oral cyanobalamin treatments caused a significant increase in serum vitamin B12 levels compared with before treatment ($p<0.001$ for both).

Conclusions: In adolescents with nutritional vitamin B12 deficiency, an oral combination of thiamine, pyridoxine, and cyanocobalamin may be preferred to parenteral cyanocobalamin because it is non-invasive and provides an increase in serum vitamin B12 levels similar to parenteral cyanocobalamin treatment.

Introduction

Vitamin B12 deficiency remains a prevalent public health concern in developing countries (1). This deficiency can be attributed to various factors, including malabsorption (as observed in pernicious anemia), congenital anomalies in transport and metabolism, and dietary insufficiency stemming from the body's inability to synthesize vitamin B. In breastfed infants, the root cause of vitamin B12 deficiency often lies in maternal vitamin B12 insufficiency (2); conversely, in older age cohorts, it primarily stems from inadequate consumption of animal-derived foods, resulting in nutritional deficiency. This deficiency is associated with the onset of various medical conditions, including hematological disorders like megaloblastic anemia, along with gastrointestinal and neurological ailments. Although parenteral cyanocobalamin administration is a conventional treatment method for vitamin B12 deficiency, the most crucial disadvantage is that it is invasive. Parenteral cyanocobalamin is a viable option across various pediatric age groups with vitamin B12 deficiency, whereas oral cyanocobalamin is restricted to patients aged 12 years and above because it is available in tablet form combined with thiamine and pyridoxine. Oral and parenteral cyanocobalamin treatments have been reported in the literature in adults with megaloblastic (3), infants of mothers with vitamin B12 deficiency, and children with megaloblastic anemia (4); however, a limited number of studies have been performed on the use of oral cyanocobalamin in the treatment of nutritional vitamin B12 deficiency in adolescents (5-7). Therefore, we aimed in the present study to compare the effectiveness of oral combined cyanocobalamin therapy with that of parenteral cyanocobalamin therapy in adolescents with nutritional vitamin B12 deficiency.

Methods

Study design and participants

This retrospective study included patients of 12-18 years who were admitted to the Pediatric Outpatient Clinics of the University of Health Sciences Türkiye, Gülhane Training and Research Hospital between 2018 and 2019. The main inclusion criteria were pre-treatment serum vitamin B12 levels <200 pg/mL (8), prescription of cyanocobalamin replacement following measurement, and post-treatment serum vitamin B12 level measurement 1 month after treatment. Patients aged younger than 12 years, with post-treatment vitamin B12 levels <200 pg/mL, who were on ongoing cyanocobalamin replacement at the time of screening, with megaloblastic anemia, severe neurological symptoms, malabsorption, iron deficiency anemia, and folate deficiency were excluded. When other causes of deficiency were eliminated, the patient was considered to have nutritional vitamin B12 deficiency. Age- and sex-adjusted anemia was defined according to the World Health Organization criteria (9). Iron and folate deficiency was defined as ferritin and folate levels below 12 and 5 ng/mL, respectively. The study was approved by the Ethics Committee of the University of Health Sciences Türkiye, Gülhane Training and Research Hospital (approval number: 2020-51, date: 25.02.2020).

Treatment protocol

As part of the existing outpatient protocol of the clinic, the cases included in the study were administered intramuscular (IM) cyanocobalamin (Dodex® ampules Deva Drug Corporation, Türkiye; 1 mL; 1000 mcg cyanocobalamin) at a dose of 100 mcg every day for a week (it was prepared by diluting 1 mL of medicine with 9 mL of physiological serum and withdrawing it into a 1 mL syringe), 1000 mcg every other day for a week, then 1000 mcg twice a week for a week, and finally 1000 mcg once a week (10). The subjects were prescribed a daily combined tablet (Apikobal® tablet, Santa Farma Drug Corporation, Türkiye) (10) containing 1 mg cyanocobalamin, 50 mg thiamine, and 250 mg pyridoxine. Oral or parenteral treatment is chosen based on the preference of the physician who evaluates the patient in the outpatient clinic. Serum vitamin B12 levels were available in all patients at the time of diagnosis and at the first month of treatment. During the study period, serum vitamin B12 levels were measured using the chemiluminescence method, a Beckman Colter DxI 800 auto-analyzer (Beckman Colter, Brea, CA, USA) at the institution of the work.

Outcomes

The primary outcome was the post-treatment difference in serum vitamin B12 levels among patients who received an oral combination of thiamine, pyridoxine, cyanocobalamin, and parenteral cyanocobalamin treatments.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism v.8.2.0. The Kolmogorov-Smirnov test was used to evaluate the conformity of the data to a normal distribution. Serum vitamin B12 levels were tested using two-way repeated measures analysis of variance (factors "treatment" and "evaluation times (before and after treatment)" and Bonferroni's multiple comparisons test. The significance level was set as at least $p<0.05$. Continuous variables were presented as means and standard error mean (SEM) while categorical variables were reported as frequencies and percentages. The significance level was set as at least $p<0.05$.

Results

Basic characteristics

The study included 85 patients with a median age of 15 [interquartile range (IQR), 14 to 16 years], girls (55.3%) with post-treatment serum vitamin B12 levels above the target level of 200 pg/mL. No biochemical findings of iron or folic acid deficiencies were noted. Parenteral cyanocobalamin was given

administered to 34 patients with a median age of 16 years (IQR, 14 to 16 years), and girls (52.9%), and oral cyanocobalamin were given to 51 patients with a median age of 15 years (IQR, 13 to 16 years), and girls (58.8%). There were no differences in the male and female rates in both groups.

Treatment results

The mean serum vitamin B12 levels before parenteral and oral cyanocobalamin treatment were 150.32±6.49 pg/mL and 132.35±4.67 pg/mL, respectively. The mean serum vitamin B12 levels after parenteral and oral cyanocobalamin treatment were 566.0±62.77 pg/mL and 463.1±36.97 pg/mL, respectively. According to the two-way repeated analysis of variance, the effects of group ($F_{1,83}$=3.258; p=0.0747) and group x time interaction ($F_{1,83}$=1.504; p=0.2235) were not statistically significant. Both parenteral and oral cyanobalamin treatments caused a significant increase in serum vitamin B12 levels in our patients compared with before treatment (p<0.001 for both) (Table 1). There was a significant difference in the time results ($F_{1,83}$=6116.3; p<0.001). Subsequently, in the post-hoc analysis performed with the Bonferroni test, no significant difference was observed between the two groups in terms of vitamin B12 levels before and after treatment (p=0.9961, p=0.068, respectively). Changes in serum vitamin B12 levels before and after treatment in the oral and parenteral cyanocobalamin treatment groups are shown in Figure 1.

No safety issue was recorded in patient files.

Discussion

Dietary deficiency is the primary cause of vitamin B12 deficiency (11), which results from insufficient consumption of animal-based foods. Vitamin B12 deficiency is also observed in breastfed infants with mothers experiencing vitamin B12 deficiency, pregnant women, and older vegetarian and vegan children who have limited intake of animal-based foods (12). Methylcobalamin, hydroxycobalamin, adenosylcobalamin, and cyanocobalamin are viable treatments for vitamin B12 deficiency. In parenteral vitamin B12 replacement, hydroxycobalamin and cyanocobalamin are administered IM. Alternatively, ampoules containing cyanocobalamin alone or combined with thiamine, pyridoxine, methylcobalamin, or adenosylcobalamin can be administered orally. There are also recommendations for the combined use of these different forms of cobalamin in the treatment of vitamin B12 deficiency (13).

Cyanocobalamin is the most widely used agent for treating vitamin B12 deficiency and can be administered via parenteral or oral routes. In conditions like pernicious anemia, a well-established dosing regimen involves an initial dose of 100 mcg/day for 1 week and a dose of 1000 mcg/day on alternate days for another week. Subsequently, the recommended dosage is 1000 g/day twice a week for one week, and finally, 1000 g/day once a week (10). Oral cyanocobalamin recommendations include daily tablets containing 1000 g of cyanocobalamin, 50 mg of thiamine, and 250 mg of pyridoxine. Alternatively, for patients unable to swallow tablets or those under six years of age, daily oral administration of ampoules containing 1000 mcg of cyanocobalamin is recommended (10). Oral cobalamin is cost-effective, safe, and convenient (14).

In children, parenteral vitamin B12 is the established treatment for megaloblastic anemia (4), neuropsychiatric disorders, absorption disorders (15,16), and metabolic disorders. Unfortunately, no standard protocol exists for oral replacement therapy to address nutritional vitamin B12 deficiency resulting from insufficient dietary intake without an underlying pathology. Parenteral therapy has several drawbacks, including elevated treatment costs, reduced efficacy, and complicated administration.

Few studies have explored the equivalentity of oral versus parenteral cyanocobalamin in the replacement therapy for

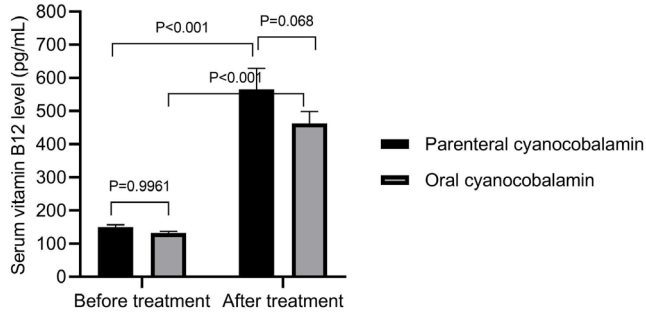

Figure 1. Changes in serum vitamin B12 levels before and after oral and parenteral cyanocobalamin treatment

Table 1. Comparison of serum vitamin B12 levels before and after parenteral and oral cyanocobalamin therapy among adolescents with vitamin B12 deficiency

Administration routes of cyanocobalamin	Before treatment (pg/mL)[e]	After treatment (pg/mL)[e]	p[Ω] value
Parenteral (n=34)	150.32±6.49	566.0±62.77	**p<0.001**
Oral (n=51)	132.35±4.67	463.1±36.97	**p<0.001**
p[Ω] value	0.9961	0.068	

[Ω]Bonferroni's multiple comparison p value.
[e]The results are expressed as mean±SEM.
SEM: Standard error of the mean

nutritional vitamin B12 deficiency among pediatric patients. Sezer et al. (10) compared the effectiveness of oral and IM cyanocobalamin in this pediatric population. Their prospective study involved 142 children, among whom 82 received oral and 60 IM cyanocobalamin. Children with serum cobalamin levels below 300 pg/mL received either parenteral or oral cyanocobalamin therapy. IM cyanocobalamin (1000 mcg) was administered at daily doses of 100 mcg for one week, followed by 1000 mcg/day on alternate days for the subsequent week, 1000 mcg/day twice a week for one week, and ultimately once a week. Mean serum cobalamin levels showed a notable increase from a pre-treatment level of 183.5±47 pg/mL to 482±318.9 pg/mL in the oral cyanocobalamin group and from 175.5±42.5 pg/mL to 838±547 pg/mL in the parenteral treatment group ($p<0.001$). Before treatment, 82 children developed anemia according to age and gender. After treatment, 14/41 and 8/41 patients still had anemia in the parenteral and oral arms, respectively. There was no significant change in the number of patients who still had anemia at the end of the first month of treatment in the parenteral and oral treatment groups. The oral and parenteral formulations successfully restored serum vitamin B12 levels to the normal range. Although vitamin B12 levels before parenteral and oral cyanocobalamin treatment were statistically similar to those in this study, the patients did not have anemia. The mean serum vitamin B12 level significantly increased after treatment, and there was no significant between-group difference. In the study by Sezer et al. (10), the research group included individuals aged 1 month to 18 years, and cyanocobalamin was provided in oral ampoules for those unable to swallow tablets and for the subgroup under six years of age. In contrast, our study focused on patients aged 12-18 years, and the cyanocobalamin used was in tablet form combined with thiamine and pyridoxine.

Bahadir et al. (17) investigated the efficacy of oral vitamin B12 supplementation in children with nutritional vitamin B12 deficiency. Their study involved 47 children aged 1 month to 17 years having serum vitamin B12 levels below 200 pg/mL. They categorized the participants into two main groups: Group 1 (1-20 months) and Group 2 (6-17 years). Subsequently, they further divided the patients into subgroups based on the duration of treatment, resulting in Groups 1A and 2A (4 months of treatment) and Groups 1B and 2B (8 months of treatment). All participants were administered 1000 µg of oral cyanocobalamin daily during the first week, every other day during the subsequent two weeks, twice a week for the subsequent two weeks, and finally once a week. The administration of high oral vitamin B12 doses significantly improved serum vitamin B12 levels in all groups, with the regimen being more effective in Group 1A and Group 1B. The correlation analysis between serum vitamin B12 levels and age at the end of treatment indicated a decreasing trend with increasing age. They found that a 4-month oral vitamin B12 supplementation (1000 µg) effectively managed nutritional vitamin B12 deficiency in children. However, dose adjustments based on body weight among older children are necessary (15). On the other hand, their study included patients aged 1 month to 17 years who received oral cyanocobalamin for 4 months, whereas our study included a population aged 12-18 years who received oral or parenteral treatment during a 4-week observation.

Tuğba-Kartal and Çağla-Mutlu (18) aimed to compare the efficacy of sublingual (SL) cyanocobalamin and methylcobalamin with IM cyanocobalamin treatment in children aged 5-18 years with vitamin B12 deficiency. They found that SL and methylcobalamin were equally effective as IM cyanocobalamin in improving serum vitamin B12 levels and addressing hematologic abnormalities. In our study, oral cyanocobalamin in tablet form showed a similar effectiveness trend, though the patient age was different.

Orhan Kiliç et al. (19) compared the efficacy of oral, SL, and IM vitamin B12 supplementation in children aged 0-3 years. They concluded that SL methylcobalamin was as effective as oral and IM cyanocobalamin in improving serum vitamin B12 levels in this age group. While SL methylcobalamin and SL cyanocobalamin have gained popularity in treating nutritional vitamin B12 deficiency, oral cyanocobalamin retains its significance due to its cost-effectiveness. In our study, methylcobalamin was not used, and the adolescent group was considered; however, oral cyanocobalamin increased serum vitamin B12 levels, similar to IM cyanocobalamin, in the adolescent group.

A Cochrane review by Wang et al. (3) indicated that oral and IM cyanocobalamin exhibited similar effects on normalizing serum vitamin B12 levels. The study results suggested that the assumption of oral cyanocobalamin's safety over IM vitamin cyanocobalamin was grounded in low-evidence studies. Consequently, high-quality research is imperative in this area. In our study, there are no safety issues related to oral and parenteral cyanocobalamin.

Our study has several limitations, including a low sample size, lack of measurement of methylmalonic acid and homocysteine levels, and absence of detailed nutritional history. A short follow-up of 4 weeks also requires confirmation of long-term.

Conclusion

In conclusion, this study found that daily oral cyanocobalamin treatment raised serum vitamin B12 levels to the normal range, similar to parenteral cyanocobalamin treatment for nutritional vitamin B12 deficiency in adolescents. Given its non-invasive, cost-effective, and user-friendly features, oral vitamin B12 administration should be encouraged, especially for parents seeking to avoid painful injections for their children. Nevertheless, further comprehensive research is warranted to confirm the long-term maintenance of serum vitamin B12 levels in this age group.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of the University of Health Sciences Türkiye, Gülhane Training and Research Hospital (approval number: 2020-51, date: 25.02.2020).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Ö.G., Concept: Ö.G., M.A., E.A., Design: Ö.G., M.A., E.A., Data Collection or Processing: Ö.G., M.A., Y.H.A., B.Ö.G., Analysis or Interpretation: M.A., F.Ü., Literature Search: Ö.G., Writing: Ö.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. McLean E, de Benoist B, Allen LH. Review of the magnitude of folate and vitamin B12 deficiencies worldwide. Food Nutr Bull. 2008;29(2 Suppl):38-51.
2. Erdeve O, Arsan S, Atasay B, Ileri T, Uysal Z. A breast-fed newborn with megaloblastic anemia-treated with the vitamin B12 supplementation of the mother. J Pediatr Hematol Oncol. 2009;31:763-765.
3. 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:CD004655.
4. Tandon R, Thacker J, Pandya U, Patel M, Tandon K. Parenteral vs Oral Vitamin B12 in Children With Nutritional Macrocytic Anemia: A Randomized Controlled Trial. Indian Pediatr. 2022;59:683-687.
5. Chandra J, Dewan P, Kumar P, et al. Diagnosis, Treatment and Prevention of Nutritional Anemia in Children: Recommendations of the Joint Committee of Pediatric Hematology-Oncology Chapter and Pediatric and Adolescent Nutrition Society of the Indian Academy of Pediatrics. Indian Pediatr. 2022;59:782-801.
6. Gupta Bansal P, Singh Toteja G, Bhatia N, et al. Deficiencies of Serum Ferritin and Vitamin B12, but not Folate, are Common in Adolescent Girls Residing in a Slum in Delhi. Int J Vitam Nutr Res. 2015;85:14-22.
7. Kapil U, Bhadoria AS. Prevalence of Folate, Ferritin and Cobalamin Deficiencies amongst Adolescent in India. J Family Med Prim Care. 2014;3:247-249.
8. Matchar DB, McCrory DC, Millington DS, Feussner JR. Performance of the serum cobalamin assay for diagnosis of cobalamin deficiency. Am J Med Sci. 1994;308:276-283.
9. Nutritional anaemias: tools for effective prevention and control. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. Last Accessed Date: 2023 July 11. Available from: https://apps.who.int/iris/bitstream/handle/10665/259425/9789241513067-eng.pdf?sequence=1&isAllowed=y
10. 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;23:653-657.
11. Balcı YI, Ergin A, Karabulut A, Polat A, Doğan M, Küçüktaşcı K. Serum vitamin B12 and folate concentrations and the effect of the Mediterranean diet on vulnerable populations. Pediatr Hematol Oncol. 2014;31:62-67.
12. Goraya JS, Kaur S, Mehra B. Neurology of Nutritional Vitamin B12 Deficiency in Infants: Case Series From India and Literature Review. J Child Neurol. 2015;30:1831-1837.
13. Thakkar K, Billa G. Treatment of vitamin B12 deficiency-methylcobalamine? Cyancobalamine? Hydroxocobalamin?-clearing the confusion. Eur J Clin Nutr. 2015;69:1-2.
14. Sanz-Cuesta T, Escortell-Mayor E, Cura-Gonzalez I, et al. Oral versus intramuscular administration of vitamin B12 for vitamin B12 deficiency in primary care: a pragmatic, randomised, non-inferiority clinical trial (OB12). BMJ Open. 2020;10:e033687.
15. Yajnik CS, Behere RV, Bhat DS, et al. A physiological dose of oral vitamin B-12 improves hematological, biochemical-metabolic indices and peripheral nerve function in B-12 deficient Indian adolescent women. PLoS One. 2019;14:e0223000.
16. 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;25:3124-3134.
17. Bahadir A, Reis PG, Erduran E. Oral vitamin B12 treatment is effective for children with nutritional vitamin B12 deficiency. J Paediatr Child Health. 2014;50:721-725.
18. Tuğba-Kartal A, Çağla-Mutlu Z. Comparison of Sublingual and Intramuscular Administration of Vitamin B12 for the Treatment of Vitamin B12 Deficiency in Children. Rev Invest Clin. 2020;72:380-385.
19. Orhan Kiliç B, Kiliç S, Şahin Eroğlu E, Gül E, Belen Apak FB. Sublingual methylcobalamin treatment is as effective as intramuscular and peroral cyanocobalamin in children age 0-3 years. Hematology. 2021;26:1013-1017.