Comparison of the efficacy of parenteral and oral treatment for nutritional vitamin B12 deficiency in children

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ABSTRACT

Objective: Although, oral replacement for vitamin B12 deficiency has been proved to be effective in adults, it is mainly treated with parenteral therapy. There are only few studies on oral replacement therapy of vitamin B12 with children. Therefore, we aimed to compare the efficacy of oral treatment with intramuscular vitamin B12 injections in pediatric population.

Methods: Children with serum cobalamin concentrations less than 300 pg/mL, were treated either with the parenteral therapy or with oral vitamin B12. The primary and secondary outcomes of the study were the normalization of serum vitamin B12 and hemoglobin at first month, respectively.

Results: Post-treatment vitamin B12 values were significantly higher than pre-treatment values (p-value <.001). Vitamin B12 increased from 183.5 ± 47 pg/mL to 482 ± 318.9 pg/mL in the oral and from 175.5 ± 42.5 pg/mL to 838 ± 547 pg/mL in the parenteral treatment arm (p-value <.001). Before treatment, 82 children had anemia according to age and gender. After treatment, 14/41 and 8/41 patients still had anemia at the first month of treatment in the parenteral and oral arms, respectively. The number of patients who still have anemia at the end of the 1st month of treatment did not significantly changed in the parenteral and oral treatment groups (p-value = .44).

Conclusions: In this study, both oral and parenteral formulations were shown to be effective in normalizing vitamin B12 levels. We suggest that oral formulations may be considered to be safe as a first line treatment for vitamin B12 deficiency in children.

KEYWORDS
Children; cyanocobalamin; oral; parenteral; vitamin B12

Introduction

Over the past decades, the incidence of vitamin B12 deficiency in children has been reported to be increased in developing countries [1]. The standard treatment of vitamin B12 deficiency is parenteral injections. Various treatment schedules and different dosing schemes have been proposed in literature, most of which initiate the treatment with frequent dosing and transit to a less frequent maintenance [2–5].

High dose of oral vitamin B12 has been used effectively for the treatment of vitamin B12 deficiency even in patients with pernicious anemia [6–9]. Oral supplementation of vitamin B12 with a daily dose of 500 mcg produces satisfactory responses in patients with vitamin B12 deficiency and daily dose of 1000 mcg produces successful long-term results in patients with intrinsic factor deficiency [7]. On the other hand, intramuscular injections are painful, prone to complications, lead to caregiver burdens, cost a lot to the health system and also most patients prefer oral treatment to injections [9]. However, single vitamin B12 oral suspension preparations are not available for children in most parts of the world.

Studies on oral treatment of vitamin B12 deficiency is mostly on adults [2–5,9]. There are few studies on oral replacement therapy of vitamin B12 in children [10–15]. Here, we aimed to compare the efficacy of oral vitamin B12 formulations and intramuscular vitamin B12 in restoring serum B12 levels in children with nutritional vitamin B12 deficiency.

Material and methods

Children aged between 1 month and 18 years old with serum vitamin B12 level under 300 pg/mL were included in this prospective study. The study was performed in the outpatient pediatric clinic from January to December 2016. Children with symptoms or signs that are related with vitamin B12 deficiency (such as failure to thrive, loss of appetite, presence of anemia, seizures, movement disorders, tingling sensations etc.) were examined and their vitamin B12 levels were measured in plasma.
Tests for complete blood counts and red cell indices were performed. A review of the peripheral smear for red cell size, fragmented cells, morphologic abnormalities and signs of hemolysis were recorded. Serum ferritin and folate levels were collected when clinically indicated. Newborns, patients with chronic diseases, patients with a history of allergic reaction to vitamin B12, patients receiving micronutrient supplementation and patients who failed to give consent were excluded from the study. Anemia was described according to World Health Organization by age and gender [16]. Leukocyte count below 4000/mm³ was regarded as leukopenia, and thrombocyte count below 100,000/mm³ as thrombocytopenia. Iron and folate deficiency was considered with ferritin and folate levels under 12 mcg/L and 5 ng/mL, respectively.

**Parenteral treatment protocol**

Children with neurological signs or symptoms who are unable to ingest oral medication, who have a known malabsorption syndrome, infants under 6 months old and patients using drugs that may affect absorption of vitamin B12 were treated with parenteral treatment protocol. For the treatment, Dodex® ampules (Deva Drug Corporation, Turkey; 1 ml; 1000 mcg cyanocobalamin) were injected 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.

**Oral treatment protocol**

Children who were able to swallow tablets were treated with a combination of multivitamin complex consisting of 50 mg thiamin, 250 mg pyridoxin and 1000 mcg cyanocobalamin (Apikobal® tablet, Santa Farma Drug Corporation, Turkey). Patients received one tablet per day up to one month. Oral vitamin B12 tablets were administered as a single tablet and at least 1 hour before meal in the fasting state.

Children under 6 years old or who are not able to swallow tablets were treated with Dodex® ampules orally with the same protocol as the parenteral arm. Ampule forms were administered by parents/caregivers in the fasted state.

Samples were collected in the fasting state, approximately 24 hours after the last dose at day 30. The primary and secondary outcomes of the study were the normalization of serum vitamin B12 levels and hemoglobin at first month. Vitamin B12 levels were measured using chemiluminescence method by ARCHITECT i2000SR immunoassay analyzer (Abbott Park, Illinois, USA). Adverse events and side effects were also followed and noted.

All patients/parents of children were informed about the study prior to enrollment and written informed consents were obtained. The study was approved by the ethics committee of Zeynep Kamil Maternity and Children’s Diseases Training and Research Hospital (Approval number: 012, Approval date: 08.01.2016).

Statistical analyses were performed by using SPSS version 17 (IBM SPSS Statistics, Chicago, IL). Intragroup comparisons for pre-treatment and post-treatment values were done by Student’s t-test for continuous paired variables. A p-value ≤ .05 was considered statistically significant.

**Results**

A total number of 142 children (66 girls and 76 boys) were included in this prospective study. Of them, 82 children were treated with oral form of vitamin B12 and 60 children were treated with i.m.formulary. Median age of patients was 24.5 months old (Range: 1 month-17 years old). Median age and the gender of the oral and parenteral groups were similar (p-value = .034 and .08, respectively). Post-treatment vitamin B12 values at one month were investigated in 54 and 53 children in parenteral and oral arms, respectively. Pre-treatment values for hemoglobin, hematocrit, MCV, vitamin B12 of the oral and parenteral groups were not significantly different (Table 1). Post-treatment vitamin B12 values in both treatment arms were significantly higher than pre-treatment values (p-value < .001). Vitamin B12 increased from 183.5 ± 47 pg/mL to 482 ± 318.9 pg/mL in the oral and from 175.5 ± 42.5 pg/mL to 838 ± 547 pg/mL in the parenteral treatment arm (p-value < .001) (Table 1).

Vitamin B12 values were categorized into three levels based on severity of deficiency. Majority of patients (97/142) had vitamin B12 levels between 100 and 200 pg/mL. Pre- and post-treatment values were compared in parenteral and oral treatment arms in all groups (Table 2).

We collected hemoglobin data of 135 patients before treatment and out of 135 patients 82 were found to have anemia before treatment according to age and gender. After the first month treatment, 14/41 and 8/41 patients were still found to have anemia in the parenteral and oral arms, respectively (p-value = .44). In total, there were 23 and 7 children with iron and folate deficiency, respectively. Seventeen children out of 23 iron deficiency and 1 child out of 7 folate deficiency had anemia. Only 3 children had iron deficiency at first month of follow-up and there were no children with folate deficiency at the first month. There were missing data on post-treatment hemoglobin of 11 patients in the oral and of 3 patients in the parenteral treatment arm.

There were 25 children with MCV values above 85 fl before treatment, but only 9 of these presented with
Table 1. Comparison of laboratory values in the oral and parenteral treatment groups in pre- and post-treatment period (mean ± SD).

| Parameter          | Parenteral group | Oral group | p-values | Parenteral group | Oral group | p-values |
|--------------------|------------------|------------|----------|------------------|------------|----------|
| Hemoglobin (g/dL)  | 11.6 ± 1.5       | 11.7 ± 1.2 | .59      | 11.8 ± 1.3       | 12.0 ± 0.9 | .22      |
| Hematocrit (%)     | 34.6 ± 4.2       | 35.3 ± 3.3 | .3       | 35.1 ± 3.4       | 35.8 ± 3.4 | .25      |
| MCV (fL)           | 79.7 ± 7.9       | 78.8 ± 6.5 | .49      | 79.2 ± 7.8       | 77.8 ± 8.6 | .37      |
| Vitamin B12 (pg/mL) | 175.5 ± 42.5     | 183.5 ± 47 | .29      | 838 ± 547        | 482 ± 318.9 | <.001    |
|                   | (83–275)         | (83–298)   |          | (279–2000)       | (156–1523) |          |

MCV: mean corpuscular volume.

Table 2. Comparison of pre-treatment and post-treatment (1st month) laboratory values, in oral and parenteral treatment protocols based on vitamin B12 levels, mean ± SD.

| Parameter          | Parenteral Treatment Group | Oral Treatment Group | p-values | p-values |
|--------------------|-----------------------------|----------------------|----------|----------|
| Vitamin B12 ≤ 100 pg/mL |                             |                      |          |          |
| n = 7              | Hemoglobin (g/dL)            | 13.6 ± 2.7           | 11.6 ± 1.1 | .19      |
|                    | MCV (fL)                    | 88.8 ± 11.9          | 87.1 ± 10.8 | .36      |
|                    | Vitamin B12                 | 94.7 ± 7.9           | 1413 ± 769 | .04      |
| Vitamin B12 >100–≤200 |                             |                      |          |          |
| n = 97             | Hemoglobin (g/dL)            | 11.2 ± 1.3           | 11.6 ± 1.3 | .006     |
|                    | MCV (fL)                    | 78.5 ± 7.8           | 78.4 ± 7.1 | .82      |
|                    | Vitamin B12                 | 164 ± 23.8           | 795 ± 513  | <.001    |
| Vitamin B12 >200–300 |                             |                      |          |          |
| n = 38             | Hemoglobin (g/dL)            | 12 ± 1.3             | 12.2 ± 1  | .63      |
|                    | MCV (fL)                    | 79.7 ± 7.3           | 79 ± 6.3   | .55      |
|                    | Vitamin B12                 | 232.8 ± 22           | 780 ± 516  | .003     |

No adverse events or side effects were detected in both groups.

Discussion

Intramuscular injections of vitamin B12 have been used as a standard treatment in vitamin B12 deficiency. Parenteral vitamin B12 rapidly and reliably restores vitamin B12 stores, and although there are studies supporting the effectiveness of oral substitution, the efficacy of oral vitamin B12 to match the same effect has been questioned. The use of oral supplements for the treatment of vitamin B12 deficiency was investigated mostly in adult patients [2–5,9]. Studies assessing the efficacy of oral vitamin B12 reported that participants responded to oral vitamin B12 replacement therapy similar to parenteral treatment [4,5,9,17,18]. Two randomized-controlled studies and a Cochrane review reported that oral vitamin B12 treatment is as effective as intramuscular administration [4,5,17,18]. In a study by Bolaman et al., elderly patients with megaloblastic anemia were randomized for a 90-day period prospectively to receive 1000 mcg cobalamin either orally or intramuscularly once daily for 10 days [4]. After 10 days, both treatments were administered once a week for 4 weeks, and after that, once a month. The mean hemoglobin and vitamin B12 concentrations were increased significantly after 90-day treatment in both groups (p < .001) [4]. Kuzminski et al. randomly assigned newly diagnosed vitamin B12 deficient patients to receive cyanocobalamin as either 1 mg intramuscularly on days 1, 3, 7, 10, 14, 16, 21, 30, 60, 90 (15 patients) or 2 mg/day orally for 120 days (18 patients) [5]. Serum cobalamin pre-treatment mean values were increased from 93 pg/mL to 1005 pg/mL in the oral group, whereas in the parenteral group, the mean value increased from 95 pg/mL to 325 pg/mL. The difference between the post-treatment values in the oral and the parenteral groups was significant (p < .005) [5]. The authors concluded that daily oral administration of 2 mg cyanocobalamin may even be better than 1 mg intramuscularly on a monthly basis [5]. In addition, serum cobalamin values were shown to be elevated steadily during 4-month oral treatment. In contrast, in the parenteral group, the mean serum cobalamin level was increased in a month, decreased at second month and remained the same at the fourth month of intramuscular therapy [5]. A randomized-controlled clinical trial in patients’ ≥65 years of age compared the efficacy of oral and intramuscular vitamin B12 treatments [2]. Patients were followed for a year with an intramuscular treatment protocol as follows: 1 mg vitamin B12 on alternate days in first two weeks, 1 mg/week in following weeks up to two months and 1 mg/month in weeks 9–52. In the oral arm, vitamin B12 was administered as: 1 mg/day in the first two months and 1 mg/week in following weeks up to a year. The authors measured serum vitamin B12 concentration at weeks 8, 26 and 52 [2]. The results of this protocol have not been published yet. In a randomized study that compared the efficacy of oral and intramuscular vitamin B12 in terms of normalizing serum concentrations, 22 patients received daily 1000 mcg oral vitamin B12 for 90 days, and 26 patients received 1000 mcg intramuscular B12 injections on study days 1, 3, 7, 10, 14, 21, 30, 60,
and 90 [3]. Both treatments resulted in normal serum cobalamin levels by day 15 in all patients [3]. In the first two weeks of the study, intramuscular regimen produced higher cobalamin values than the oral treatment. On day 15 of study, mean serum cobalamin levels were 2434 pg/mL for the parenteral group and 1687 pg/mL for the oral group (p = .02). The mean value of serum cobalamin concentrations at days 61, and 91 following parenteral treatment was higher than oral treatment levels but this was not statistically significant [3]. Efficacy of oral vitamin B12 replacement was also studied in gastric cancer patients after total gastrectomy [8]. Daily oral vitamin B12 administration for 3 months was compared with intramuscular vitamin B12 injections weekly for 5 weeks and monthly thereafter for a total of 3 months [8]. Serum vitamin B12 levels were continuously increased during the 3 months of treatment. In contrast, the mean serum vitamin B12 levels peaked after the weekly intramuscular injections, but decreased at second month and remained stable at third month [8]. For maintenance therapy of vitamin B12 deficiency, 1000 μg tablet of cyanocobalamin was reported to be safe in different studies [3,9].

Macrocytic anemia is confined to a severe and long-standing cobalamin deficiency in infants [19]. Jenssen et al. reported that cobalamin supplementation improved all markers of impaired cobalamin function but had no effect on hematological cell counts at 4 months in infants [20]. Despite a biomarker profile of moderate cobalamin deficiency, growth of infants was not affected [20]. A lower iron status was found to be the main determinant of hematological parameters [20]. In support of this hypothesis, in our study, although vitamin B12 increased in all children, changes in mean hemoglobin and MCV levels were seen in a limited group. This can be due to the time needed for effective hematopoesis, a follow-up duration of 1 month in our study may not be enough to show the effects on hematological parameters.

Few studies on oral treatment of vitamin B12 deficiency in children reported significant improvement in serum vitamin B12 levels as well [10–15]. Bahadır et al. reported 48 children treated with oral vitamin B12 with the following protocol: 1000 mcg every day for a week, every other day for 2 weeks, 2 days a week for 2 weeks and then followed with once a week [10]. This protocol was shown to be effective in all children for achieving normal vitamin B12 levels [10]. In another study with 14 children with selective vitamin B12 malabsorption, oral administration of 1000 mcg of vitamin B12 every 2 weeks was shown to be adequate to stabilize hematological parameters, serum vitamin B12 levels and treat anemia [11]. Sezer et al. treated 79 vitamin B12 deficient children orally and showed that the mean pre-treatment vitamin B12 level was increased from 182 ± 47.6 pg/mL to 482 ± 318 pg/mL after 1 month of treatment [13]. Oral cyanocobalamin was found to be effective for the treatment of vitamin B12 deficiency [13].

In a study conducted by Chandelia et al., children with nutritional anemia (n = 150) were randomized to receive iron, folic acid or iron, folic acid and cobalamin [12]. Cobalamin levels were tested in 41 children and 97.5% had cobalamin deficiency. Cobalamin was administered as either oral tablets daily or intramuscular injections for the treatment. Treatment protocols were as follows; oral group: 125 μg, 250 μg and 500 μg for children under 1 y, 1–2 y or older than 2 y, respectively; parenteral group: 250 μg or 500 μg for children younger than 2 y and 2–5 y respectively; on days 1, 15 and 29. At 2, 4, and 8 weeks, hemoglobin levels were measured and higher hemoglobin levels were observed in the cobalamin group. However, there was no statistically significant difference between oral and parenteral arms [12]. The authors reported that oral administration is as effective as intermittent parenteral administration [12]. Verma et al. treated 28 children aged between 6 months and 18 years with macrocytic anemia [14]. Oral treatment consisted of 500 mcg tablet of methylcobalamin once daily at a dosage of 30 mcg/kg/day [14]. The authors demonstrated the hematological and biochemical response to oral vitamin B12 therapy at 1 month with a mean increase in hemoglobin, absolute reticulocyte count, platelets, holotranscobalamin and vitamin B12 levels, also with mean fall in mean corpuscular volume [14]. Post-treatment correction of vitamin B12 levels was observed in all the children [14].

The serum level of vitamin B12 is very sensitive under 100 pg/mL, but between 100 and 300 pg/mL, the sensitivity decreases [21]. Metabolic evidence of vitamin B12 deficiency is frequently demonstrated with serum vitamin B12 levels under 300 pg/mL [22,23]. Serum vitamin B12 levels under 350 pg/mL is reported to be 90% sensitive for diagnosing vitamin B12 deficiency [24]. Thus, we considered vitamin B12 deficiency under 300 pg/mL in our study.

Parenteral injections in our study caused a dramatic increase in vitamin B12 levels. Daily administration of oral vitamin B12 also maintained a consistent serum level, whereas injections resulted in peaks and caused fluctuations in cobalamin status [3]. We used oral cyanocobalamin in this study. In Turkey, the methycobalamin containing brand consists of both methylcobalamin and vitamin B6 vials in the same box with different colors. This sometimes causes a confusion among patients and medical teams and mistreatment may potentially occur. For this reason, cyanocobalamin is chosen at our center to avoid medication errors. Also, in our country, the only form of sole vitamin B12 is the intravenous ampules, whereas oral tablets containing vitamin B12 mostly consist of other vitamins and elements.
The limitation of our study is that we did not investigate methyllumalic acid and homocysteine levels. Also we do not have the long-term results of vitamin B12 levels in both groups. Evidence for long-term effectiveness of oral treatment needs to be studied for confirmation of efficacy.

**Conclusion**

In conclusion, both oral and parenteral formulations are found to be effective in normalizing vitamin B12 levels in children with nutritional vitamin B12 deficiency. We suggest that oral formulations may be considered as a first line treatment for vitamin B12 deficiency in children.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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