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Sublingual spray treatment of vitamin B12 deficiency in children

Ali Osman Koksal [1]*, Tulin Koksal [1], Aysu Duyan Camurdan [2]

[1] Ambulatory Pediatric Clinic, Ankara, TURKEY
[2] Department of Social Paediatrics, Faculty of Medicine, Gazi University, Ankara, TURKEY
***Corresponding Author:** koksal6623@gmail.com

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ABSTRACT

Objective: Vitamin B12 deficiency can lead to serious health problems both in children and adult. Intramuscular injection therapy is applied as the gold standard in the treatment of vitamin B12 deficiency. There are also oral, nasal, and sublingual spray treatment methods. In this study, we aimed to show the efficacy of sublingual spray treatment of vitamin B12 deficiency in children.

Materials and Methods: Forty-five pediatric patients (25 boys, 20 girls), aged 9-36 months with serum cobalamin concentrations less than 200 pg/mL, were treated with sublingual vitamin B12 (methylcobalamin) spray. All patients were treated for four months by giving 500 µg oral spray daily for the first week, every other day for the next one week, two days a week for the next two weeks and then once a week for four months. Vitamin B12 levels were checked after four months.

Results: Post-treatment vitamin B12 values were significantly higher than pre-treatment values ($p<0.001$). Vitamin B12 levels increased from 161.58±32.98 pg/mL to 427.44±148.58 pg/mL. After the treatment, the vitamin B12 level of all patients was found to be >200 pg/mL, except for only two patients. Vitamin B12 levels returned to normal in 96% of the patients with a sublingual spray treatment.

Conclusions: Data from this study indicate that sublingual vitamin B12(methylcobalamin) spray (500µg) for four months is effective for treatment of children with vitamin B12 deficiency. Sublingual spray that is easier and more practical to use can be preferred for children with vitamin B12 deficiency instead of parenteral and oral vitamin B12 therapy.

Keywords: child, methylcobalamin, vitamin B12, sublingual spray

INTRODUCTION

Recently, it has been determined that the incidence of vitamin B12 deficiency in children is increasing in developing countries. Vitamin B12 functions as a coenzyme in the metabolism of methylmalonic acid and homocysteine, which are the most abundant in the central nervous system and bone marrow [1].

Vitamin B12 is found in animal-source foods (such as meat, milk, dairy products, eggs, etc.). Vitamin B12 deficiency in children is mostly seen due to insufficient consumption of animal-source foods, malabsorption, or a congenital deficiency of one of the vitamin B12 proteins. The most common cause of vitamin B12 deficiency in children under one year of age is secondary to maternal deficiency. As a result of breastfeeding of the mother with vitamin B12 deficiency, vitamin B12 deficiency develops in the infants also. Megaloblastic anemia, growth retardation, weakness, and neurological symptoms (such as hypotonia, lethargy, irritability, coma, etc.) can be observed in children with vitamin B12 deficiency [2]. Intramuscular injection therapy is applied as the gold standard in the treatment of vitamin B12 deficiency. There are also other treatment methods including oral, nasal, and sublingual spray treatments [2]. It can increase serum levels by three to 10 times more orally, as the drug is more rapidly absorbed into the blood by sublingual absorption. Absorption occurs through numerous capillaries under the tongue [3].

Sublingual spray application is considered an easier and more comfortable method compared to intramuscular, oral, and nasal treatment applications in children with vitamin B12 deficiency. In this study, the treatment results of B12 deficiency cases treated with sublingual spray were evaluated.

MATERIALS AND METHODS

Forty-five pediatric patients (25 boys, 20 girls) with vitamin B12 deficiency treated with sublingual methylcobalamin spray were evaluated retrospectively. The study was executed in an ambulatory pediatric clinic between January the years of 2020-2022. Children aged 9-36 months with serum vitamin B12 levels below 200 pg/mL were included in this study. Serum vitamin B12 levels between 200-700 pg/mL were considered a normal level. Blood tests were taken for control purposes from patients who came for routine follow-up and did not have any complaints. Plasma vitamin B12 (cobalamin) concentrations were determined with the electro-chemiluminescence method

(Cobas electro-chemiluminescence kit, Roche Diagnostic, Indianapolis, Indiana). Children whose families did not give consent, who had a chronic disease, and who were older than 36 months were excluded from the study.

Complete blood count and peripheral smear examination for erythrocyte size, lysed cells, morphological abnormalities, and signs of hemolysis were performed.

Sublingual Spray Treatment Protocol

Ocean Methyl B12® Spray (Orzax Drug Corporation, Turkey) was used for sublingual spray application of vitamin B12. There are 500 µg of vitamin B12 (methylcobalamin), deionized water, bulking agent: glycerol, maltodextrin; preservative: potassium sorbate) in a single puff. We applied treatment according to the protocol recommended by the Turkish Pediatric Hematology Society [4].

All patients were treated for four months by giving 500 µg oral spray daily for the first week, every other day for the next one week, two days a week for the next two weeks and then once a week for four months. Vitamin B12 levels were checked after four months. All parents were informed about the study and their written consent was obtained. The research was conducted following ethical procedures.

Statistical Analysis

Statistical package for social sciences (SPSS), version 22.0 for Windows (SPSS Inc., Chicago, IL, USA) computer package program was used for statistical analysis of research data. Data were expressed as mean ± standard deviation. The levels of B12 and other values were normally distributed.

The Kolmogorov-Smirnov was used to verify normal distribution of vitamin B12 and other values. Within-group comparisons for pre-treatment and post-treatment values were made with the continuous paired variables student's t-test. In this study, the statistical significance level was accepted as <0.05.

RESULTS

A total of 45 children (20 girls/25 boys) were included in this study. The mean age (±SD) of the children was 14.7 (±2.2) months. Pre- and post-treatment values for hemoglobin, mean corpuscular volume (MCV), and vitamin B12 are shown in **Table 1**. The changes in hemoglobin (pre-treatment: 11.69 (±1.074)g/dl; post-treatment: 12.39 (±0.761)g/dl) and MCV (pre-treatment: 75.9 (±9.15)fL; post-treatment: 78.89 (±5.98)fL) values before and after treatment were not statistically significant (p>0.05). Post-treatment vitamin B12 values were significantly higher than pre-treatment values (p<0.001). Vitamin B12 levels increased from 161.58 (±32.98) pg/mL to 427.44 (±148.58) pg/mL (**Figure 1**, **Figure 2**, and **Figure 3**).

None of the children had leukopenia, thrombocytopenia, or pancytopenia. None of the peripheral blood smear examinations showed signs of hemolytic anemia or hemoglobinopathy. No treatment-induced side effects were detected in the patients. After the treatment, the vitamin B12 level of all patients was found to be >200 pg/mL, except for only two patients. Vitamin B12 levels returned to normal in 96% of the patients with a sublingual spray treatment.

Table 1. Comparison: Pre- & post-treatment laboratory values

	Pre-treatment*	Post-treatment*	p-value
Hemoglobin (g/dL)	11.69±1.074 (8.9-13.4)	12.39±0.76 (10.6-13.8)	0.061
MCV** (fL)	75.96±9.15 (50-107)	78.89±5.98 (57-89)	0.067
Vitamin B12 (pg/mL)	161.58±32.98 (73-199)	427.44±148.58 (195-914)	<0.001

Note. *Mean±SD (minimum-maximum); **Mean corpuscular volume

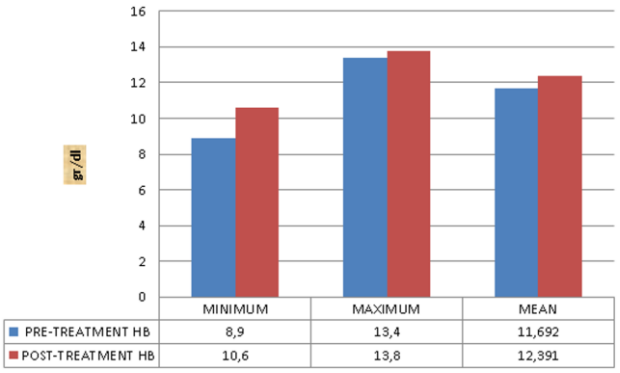

Figure 1. Hemoglobin laboratory values: Pre- & post-treatment

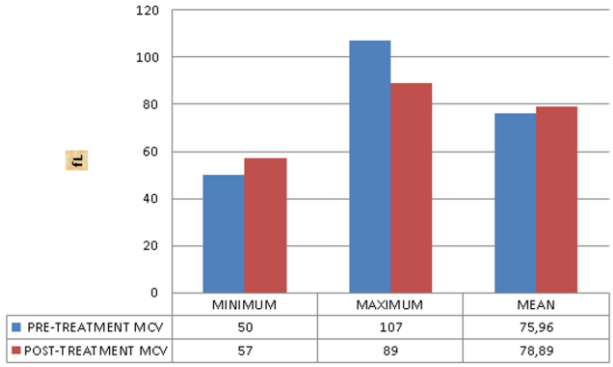

Figure 2. MCV laboratory values: Pre- & post-treatment

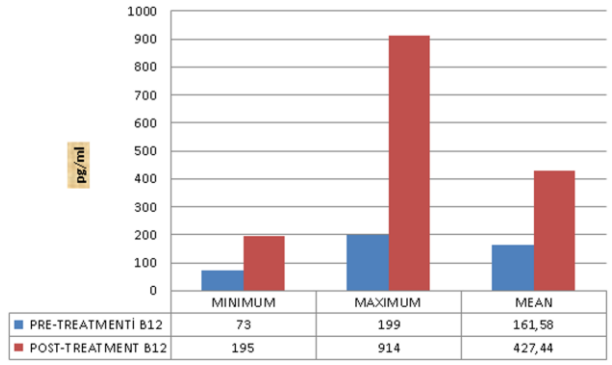

Figure 3. Vitamin B12 laboratory values: Pre- & post-treatment

DISCUSSION AND CONCLUSIONS

Intramuscular injection of vitamin B12 (cyanocobalamin) has been applied as the gold standard for years in the treatment of vitamin B12 deficiency. Parenteral B12 administration increases vitamin levels rapidly and reliably [5]. There are studies on oral B12 therapy in vitamin B12 deficiency, mostly in adult patients [6-10]. Moreover, there are many studies demonstrating that the effectiveness of oral vitamin B12 therapy is similar to parenteral therapy [8-11]. According to cochrane data, oral vitamin B12 therapy was stated to be as effective as intramuscular administration [12].

We think that the use of oral spray instead of painful and stressful intramuscular injection may be a promising alternative in the treatment of vitamin B12 deficiency in

children. It is also a fact that pharmacologically, the bioavailability of sublingual spray is more effective than oral treatment. We evaluated the results of 45 patients treated with methylcobalamin sublingual spray according to the treatment protocol [4] recommended by the Turkish Pediatric Hematology Society.

A study was performed to investigate the effectiveness of oral Vit-B12 (cyanocobalamin) treatment in children with vitamin B12 deficiency following the protocol of the Turkish Pediatric Hematology Society [13]. In this study, children under the age of two were administered orally 1,000 µg/day on an empty stomach for one week, 1,000 µg/day every other day for one week, 1,000 µg/day two days a week for two weeks and 1,000 µg/day once a week for four months. It was stated that the four-month maintenance treatment would be sufficient and effective. In our study, we used 500 µg/day sublingual spray vit-B12 (methylcobalamin) with the same protocol. Although we used half of the drug dose used in the study of [13], we think that we obtained positive results because sublingual spray absorption is faster than intestinal absorption.

Since the absorption of the drug in the form of sublingual spray and its passage into the blood is much faster, it can increase serum levels three to 10 times more orally. In another study [9], oral vitamin B12 therapy was found to be more effective than parenteral therapy. In this study, the efficacy of intramuscular cyanocobalamin treatment at a dose of 1,000 µg/day and oral cyanocobalamin treatment (1, 3, 7, 10, 14, 21, 30, 60, and 90 days) at a dose of 2,000 µg/day for 120 days were compared. The effectiveness of the oral treatment group compared to the intramuscular treatment group was found to be statistically significant.

There are few studies in the literature that reveal how long and at what dose oral vitamin B12 can be used in children with vitamin B12 deficiency [13, 14]. There is no standardized protocol for this treatment. Thus, the publication of the results of different application protocols will contribute to both the literature and practical use.

In studies on oral vitamin B12 therapy, the age range of children was kept very wide (one month-17 years) [13], (one month-18 years) [14]. In our study, a more specific age group (9-36 months) was preferred. We think that sublingual spray therapy can be used effectively in children who are fed more dependent on their mothers during this period, since it is easier to apply, and the results are much more satisfactory.

In [15], intranasal hydroxocobalamin therapy was applied to 10 patients aged 3-17 years with vitamin B12 deficiency. It was determined that B12 levels increased significantly in an average of 101 days during their follow-up process. However, this study was carried out with a small number of patients and there is uncertainty about how intranasal administration will affect the nasal mucosa in the long term [15]. The possibility of local changes in intranasal spray application can be considered as a disadvantage of this treatment method. We did not encounter any changes in the oral mucosa in the control examinations of the patients to whom we used the sublingual spray. In addition, the fact that we did not receive any negative feedback from the patients during the treatment suggests that this method is an easily applicable treatment method in children. More and larger studies are required to be executed on this subject.

Limitations

Non-examining of methylmalonic acid and homocysteine levels is one of the limitations of our study. Among the reasons why these tests cannot be performed on children with low B12 levels are that these tests were not among the routine tests we performed on healthy children who came for follow up, the family did not allow blood sampling again, and the tests were costly, creating a financial burden for the family.

To evaluate the efficacy of the treatment, we examined the hemoglobin, MCV, and vitamin B12 values before and after the treatment. We think that it is also a limitation that after performing analysis on our patients at the end of the treatment, we did not test again to evaluate the long-term results of vitamin B12 treatment. The small number of cases is another limitation of our study. It would be better if patients who received intramuscular treatment could be selected as the control group. We could not create such a group because intramuscular injection is painful and stressful for children. More extensive and long-term studies can be done to confirm the effectiveness of sublingual spray therapy.

As a result, a sublingual spray that is easier and more practical to use can be preferred for children with vitamin B12 deficiency instead of parenteral and oral vitamin B12 therapy. We hope that sublingual B12 spray therapy in children can be used easily as a child-friendly and innovative method. More comprehensive studies are required to demonstrate the efficacy of sublingual B12 spray use in children.

Author contributions: All authors have sufficiently contributed to the study, and agreed with the results and conclusions.

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Ethical statement: Ethics committee approval was not obtained as the study was a retrospective study. Since it is a study based on patient files, only the consent of the patients was obtained.

Declaration of interest: No conflict of interest is declared by authors.

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