The Efficacy, Dose and Interval Of Sublingual Methylcobalamin Spray in Children: A Single-Center Experience

Dilaltı metilkobalamin spreyin çocuklardaki etkinliği, dozu ve veriliş sıklığı: tek merkez deneyimi

Hatice Mine Çakmak[1], Yaşar Bildirici[2]

[1] Duzce University School of Medicine, Department of Pediatrics, Duzce, Turkey

[2] Eskisehir City Hospital, Department of Pediatrics, Eskisehir, Turkey

ABSTRACT

Introduction: Vitamin B12 deficiency is essential to treat because of hematologic and neurologic results. Sublingual methylcobalamin spray leads to easy, safe, and cost-effective treatment. However, studies reveal the different duration of treatment; age-specific dose is not precise. Here, we aimed to investigate the efficacy, dose adjustment, and durability of vitamin-B12 spray.

Methods: This retrospective study includes seventeen children (3 months-17 years) diagnosed with nutritional Vitamin-B12 deficiency between January 2020- January 2021. The methylcobalamin doses were 500 mcg (<1 year of age) and 1000 mcg (≥1 year of age) every day for the first week and every other day for seven weeks. In addition, serum Vitamin B12 and hemoglobin levels were studied at diagnosis and second, sixth, and twelfth months of treatment. Finally, we compared the beginning hemoglobin and Vitamin-B12 levels with the second month's values.

Results: After two months of sublingual methylcobalamin treatment, the Vitamin B12 significantly increased (p=**0.008)** and kept normal ranges for twelve months. Hemoglobin levels tended to rise in two months, but the difference was not statistically significant (p=0.22).

Conclusion: There is no consensus on the sublingual methylcobalamin dose and treatment schedule. However, we suggest that a 500 mcg dose of methylcobalamin for <1 year of age and a 1000 mcg dose for ≥ 1 year with two months treatment period is appropriate and safe for nutritional Vitamin B12 deficiency.

Key words: Child, Vitamin B12 deficiency, Vitamin B12

ÖZET

Giriş: Vitamin B12 eksikliğinin tedavisi, hematolojik ve nörolojik sonuçları nedeniyle çok önemlidir. Dilaltı metilkobalamin, kolay uygulama, güvenilir ve ucuz bir tedavidir. Çocuklarda, değişik doz, uygulama ve tedavi süreleri bildirilmiştir. Bu çalışmanın amacı, metil kobalaminin etkinliğini, doz ayarlamasını ve etkinliğini devam ettirebilirliğini araştırmaktır.

Yöntemler: Bu retrospektif çalışmaya, Ocak 2020-Ocak 2021 tarihleri arasında bir çocuk hematoloji-onkoloji polikliniğinde Vitamin B12 eksikliği tanısı almış on yedi hasta (3 ay-17 yaş) dahil edildi. Bir yaş altına 500 mikrogram, 1 yaş ve üzerine 1000 mikrogram dilaltı metilkobalamin sprey, ilk hafta her gün, sonraki yedi hafta iki günde bir uygulandı. Serum vitamin B12 ve hemoglobin değerleri tanıda, tedavinin ikinci, altıncı ve onikinci aylarında alındı. Tanıdaki ve ikinci aydaki Vitamin B12 ve hemoglobin değerleri karşılaştırıldı.

Bulgular: İki ay dilatı metilkobalamin tedavisi sonrasında, vitamin B12 düzeyinde anlamlı artış gözlendi (p=0,008), oniki aylık izlemde serum vitamin B12 düzeyi normal değerlerini korudu. Tedavinin ikinci ayında, hemoglobin değerleri yükselme eğiliminde idi. Ancak, bu fark istatistiksel anlamlı bulunmadı (p=0.22).

Sonuç: Çocuklarda Vitamin B12 eksikliği tedavisinde metilkobalaminin dozu ve tedavi süresi konusunda fikir birliği bulunmamaktadır. Biz bu çalışmada, nutrisyonel B12 eksikliği bulunan çocuklarda 1 yaş altı çocuklarda 500 mikrogram, 1 yaş ve üzeri için 1000 mikrogramın iki aylık tedavi ile etkin ve güvenilir olduğunu bildirmekteyiz.

Anahtar Kelimeler: Çocuk, Vitamin B12 eksikliği, Vitamin B12

INTRODUCTION

Vitamin B12 has an essential role in DNA and RNA synthesis. Its deficiency causes impaired cell division, megaloblastic anemia, and neurologic findings. WHO defined vitamin "B12 adequacy" as >221 pmol/L, "lowB12," as between 148 and 221 pmol/L, "B12 deficiency" as lower than 148 pmol/L. First, the physician must investigate the underlying etiology. Inadequate intake, gastrointestinal problems, pancreatitis, drugs, inherited transcobalamin deficiencies are the causes. Serum cobalamin levels are the initial diagnosis and mean cell volume; blood

Corresponding author: Hatice Mine Cakmak, Duzce University School of Medicine, Pediatric Hematology-Oncology, Duzce/Turkey
E-mail: h.m.tokuc@hotmail.com
Eskisehir Med. J. 2022; 3(3):259-263.
Received date:27.04.2022 Accepted date:08.07.2022
Authors: Hatice Mine Çakmak (ORCID: 0000-0003-3730-0982), Yaşar Bildirici (ORCID: 0000-0002-4784-7810)

film is also necessary. Serum homocysteine, holotranscobalamin, and methylmalonic acid (MMA) levels are additional for unexact diagnosis. Serum vitamin B12 is the first-line, serum MMA and homocysteine levels are the second-line (1,2,3).

Cyanocobalamin and methylcobalamin (cyanocobalamin in the United States; hydroxocobalamin in Europe) are commonly used for Vitamin B12 deficiency treatment. The duration of therapy and the route of administration differ in different etiologies. Initial parenteral therapy is the leading treatment for exceptional cases. These indications are symptomatic anemia, neuropsychiatric or neurologic symptoms, possible malabsorption, concern about follow-up. Parenteral therapy is given every other day for 1 to 2 weeks, followed by weekly injections for a month, and after one month, the administration frequency is dropped to once a month. Oral and sublingual therapies are the other treatment options (2,3).

In Vitamin B12 deficiency, methylcobalamin and adenosylcobalamin studies revealed effective results (4). Furthermore, the normalization of serum B12 is possible with sublingual therapy, improving neurological status (5). However, there are a few studies about methylcobalamin dose and efficacy in children. Here we aim to criticize the effect of methylcobalamin oral spray in Vitamin B12 deficient children aged three months-18 years.

METHODS

Seventeen patients (3 months-18 years of age) with Vitamin B12 deficiency are included in this retrospective study. These patients applied to the pediatric hematology-oncology policlinic at a tertiary center between January 2020-January 2021. They had Vitamin B12 deficiency (serum vitamin B12<200 pg/mL) and received methylcobalamin sublingual spray for two months. The daily dose of 500 mcg/day (for <1 year) and 1000 mcg/day (≥1 year) was given every day for the first week and every other day for seven weeks.

We checked serum Vitamin-B12 levels after the second, sixth, and twelfth-month of diagnosis. In addition, we studied metabolic tests (serum homocysteine and urine MMA levels) for the patients having vitamin-B12 levels near the lower limits of normal. Exclusion criteria included chronic diseases, iron deficiency, folic acid deficiency, renal disorders, drug-related malabsorption.

Statistical Analysis

We analyzed the data by IBM SPSS V23 and used The Shapiro-Wilk test to determine the suitability for the normal distribution. In addition, the Wilcoxon test compared the average and non-distributed B12 values at different months. Finally, the two-sample t-test compared the hemoglobin level at diagnosis and the second month of treatment. Average ± SD shows the quantitative data. In addition, categorical data in the form of deviation and median (minimum-maximum) were presented as frequency and percentage. A $p<0.050$ is reported as statistically significant.

Table 1. Age distribution and blood films of Vitamin-B12 deficient patients

	Frequency (n)	Percent (%)
Sex		
Male	11	64.7
Female	6	35.3
Blood films at diagnosis		
Normal	11	78.6
Megaloblastosis	3	21.4

RESULTS

Of seventeen patients with serum Vitamin B12 deficiency, eleven (64.7%) were male, and six (6%) were female. Blood film revealed megaloblastic changes in three (21.4%); others had standard blood film (Table 1). None had neurological impairment.

The mean age ± SD was 4.3±5.9, and the patients were aged between 3 months and 17 years. Serum vitamin

Table 2. Laboratory values at diagnosis and follow-up, age

	n	Mean	SD	Median	Minimum	Maximum
Age	17	4.3	5.9	1.0	0.2	17.0
Serum VB12 (pg/ml) at diagnosis	15	161.4	27.3	178	114	190.6
Serum VB12 (pg/ml) at the second month	11	555.5	505.2	338	237	1986
Serum VB12 (pg/ml) at the sixth month	3	264.0	23.4	252	249	291
Serum VB12 (pg/ml) at the twelfth month	4	301.3	25.7	312	263	318
Hb (g/dl) at diagnosis	16	10.9	2.2	10.8	7.5	14.5
Hb (g/dl) at the second month	10	11.8	1.1	11.4	10.7	14.4
Hb (g/dl) at the sixth month	3	12.3	0.6	12.2	11.8	12.9
Hb (g/dl) at the twelfth month	3	12.7	2.0	11.7	11.4	15
Urine MMA (mg/g)	6	1.4	0.3	1.4	1.1	2
Serum homocysteine (micromole/L)	11	8.0	3.1	7.4	4.5	12.8

Abb: VB12: vitamin B12, Hb: hemoglobin, MMA: methylmalonic acid

B12 levels with a mean±SD of 161.1±27.3 increased within two months of treatment to a mean±SD 555.5±505.2. The 500 microgram/day methylcobalamin dose for <1 year of age and 1000 mcg/day for others achieved the normalization of serum vitamin B12 levels with a mean of 612.2 [305-1986] pg/ml at the second month of treatment. None needed vitamin B12 replacement after the second month. The vitamin B12 levels maintained normal ranges at the sixth and twelfth months. Serum Vitamin homocysteine (micromole/L) (n=11) had a median of 7.4 [4.5-12.8]. The upper limit of serum homocysteine varies with age. Urine MMA level (n=6) was 1.4±0.3 mg/g (Table 2). No adverse event is reported among seventeen patients.

The median serum Vitamin B12 levels were higher at the second month of methylcobalamin sublingual treatment as (338 [305 - 1986]) than the median levels at diagnosis (178 [118 – 190.6]) (p=0.008). On the other hand, the mean hemoglobin levels at diagnosis (10.9 ± 1.6) and the second month (11.5 ± 0.6) were statistically similar, but it tends to increase after two months of treatment (p=0.029) (Table 3).

DISCUSSION

As a coenzyme form of cyanocobalamin, methylcobalamin has an essential role in hematopoiesis and neurologic development. Adenosylcobalamin's function is metabolic, and it has a position in myelin synthesis. Hydroxocobalamin (HCbl) lacks the cyanide moiety and has a hydroxyl group. Therefore, in hematological and neurological impairment, cyanocobalamin is the first-line treatment. High-dose oral cobalamin (2000 mcg) has comparable results with intramuscular forms. In the oral route, about 500–750 µg of each, MeCbl and AdCbl is essential (6).

A Cochrane database review includes adult Vitamin B12 studies' results. Three randomized control trials compared oral and intramuscular vitamin-B12. The blood levels were similar in two studies comparing 1000 mcg oral vs. intramuscular Vitamin B12. One of these studies completed the oral doses for three months. In another trial comparing 1000 mcg/dose (total 90 mgr) oral vitamin B12 and 1000 mcg/dose intramuscular vitamin B12, the number of participants achieving normal Vitamin B12 levels were statistically similar. One trial reached higher blood levels with 2000 mcg than intramuscular form. However, the results were identical. (7). Another adult study compared sublingual and

Table 3. Comparison of serum vitamin B12 levels and hemoglobin levels at diagnosis and the second month of follow-up

	At diagnosis		At the second month of diagnosis		p
	Mean ± SD	Median(min. - max.)	Mean ± SD	Median (min. - max.)	
Serum VB12 (pg/ml) (n=9)	161,1 ± 27,3	178 (118 – 190.6)	612.1 ± 546.1	338 (305 - 1986)	**0,008***
Hb (g/dl) (n=9)	10.9 ± 1.6	10.6 (8.7 – 13.3)	11.5 ± 0.6	11.4 (10.7 – 12.5)	0,229**

**Wilcoxon test, **Two samples t-test*

intramuscular cyanocobalamin. An intramuscular dose (1000 mcg) was administered every other day for two weeks and then once a week for four weeks. Sublingual administration was at least two packages (each containing 120 tablets) for six months. Sublingual Vitamin B12 had promising results (8).

In children, the sublingual treatment data is limited. However, a study of 47 children revealed successful results with 1000 mcg oral vitamin B12 for four months (9). Another prospective study included twenty-eight children with macrocytic anemia, Vitamin B12 deficiency, and low levels of holotranscobalamin. The patients took 500-μg methylcobalamin tablets once daily at a dosage of 30 μg/kg/day. The one-month treatment was adequate to raise Vitamin-B12 levels (10).

In one retrospective study (n=129), Kartal et al. compared the efficacy of intramuscular and sublingual Vitamin B12 preparations in children (5-18 ages). In one month of treatment, sublingual methylcobalamin (n=39) achieved similar Vitamin B12 levels with intramuscular Vitamin B12 (n=47). However, oral cyanocobalamin (n=43) could not raise the serum Vitamin-B12 levels compared with other treatments. Therefore, this study suggested that sublingual methylcobalamin can be preferred as a first-line treatment in Vitamin-B12 deficient children. Methylcobalamin dose was here 1000 mcg/dose every day for the first week, and then every other day for three weeks (11).

In another study, children aged between 0-3 years (n=159) took Vitamin-B12. Similarly, three groups were compared, sublingual methylcobalamin 1000 mcg/day every day for the first week, every other day for two weeks, two days a week for two weeks, followed by once a week for three months. Sublingual cyanocobalamin, intramuscular cyanocobalamin, sublingual methylcobalamin increased Vitamin B12 levels significantly after three months of treatment. Additionally, hemoglobin levels raised considerably in the oral cyanocobalamin group (12).

In the other study, including children (6-12 months), oral methylcobalamin with a dose of 1000 mcg was administered every day in the first week, every other day in the second week, twice a week in the third, and once a week in the last week. Again, no side effects such as vomiting or rash were reported. However, the difference between Vitamin B12 levels before and after the sublingual treatment was significant after one month of treatment (13).

In the literature, dose and administration period and type of sublingual vitamin-B12 are not standard in children. Therefore, the duration of treatment varies between one to two months. One hundred microgram/dose is used in these children's studies with different administration periods (10,11,12,13).

Our study shows the efficacy of methylcobalamin sublingual spray among children with a dose of 500 mcg below one year and 1000 mcg for ≥ one year of age. The treatment duration was two months. The cut of the level is 200 pg/ml for treatment. At the second

month of treatment, vitamin b12 levels significantly increased to a median level of 338,0 (305,0 - 1986,0) and achieved normalization up to the twelfth month of follow-up. We report here no side effects similar to the other children's studies.

The limitation of our study is including a few patients (n=17). In addition, we could not follow up all for twelve months because of drop-ups. Nevertheless, unlike the other studies, we used 500 mcg/dose of methylcobalamin for all infants and got the expected results after two months of treatment.

CONCLUSION

In nutritional Vitamin-B12 deficient infants (<1 year) without neurological compromise, a sublingual methylcobalamin spray dose 500 mcg is effective and safe. Again for children aged 1-18 years, that treatment is also effective, secure, and has consistent results up to twelve months with dietary recommendations. New prospective randomized controlled trials are needed for exact dose and duration recommendation.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Any company or institution has not financially contributed to the study.

REFERENCES

1. Devalia V, Hamilton MS, Molloy AM; British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 2014;166(4):496-513.
2. Green R. Vitamin B_{12} deficiency from the perspective of a practicing hematologist. Blood. 2017;129(19):2603-2611.
3. Hannibal L, Lysne V, Bjørke-Monsen AL, Behringer S, et al. Biomarkers and Algorithms for the Diagnosis of Vitamin B12 Deficiency. Front Mol Biosci. 2016;3 (27):1-16.
4. Sobczyńska-Malefora A, Delvin E, McCaddon A, Ahmadi KR, Harrington DJ. Vitamin B_{12} status in health and disease: a critical review. Diagnosis of deficiency and insufficiency - clinical and laboratory pitfalls. Crit Rev Clin Lab Sci. 2021;58(6):399-429.
5. 5. Chan CQ, Low LL, Lee KH. Oral Vitamin B12 Replacement for the Treatment of Pernicious Anemia. Front Med (Lausanne). 2016;3(38):1-6.
6. Thakkar K, Billa G. Treatment of vitamin B12 deficiency-methylcobalamin? Cyanocobalamin? Hydroxocobalamin?-clearing the confusion. Eur J Clin Nutr 2015;69(1): 1-2.
7. Vidal-Alaball J, Butler CC, Cannings-John R, Goringe A, Hood K, McCaddon A, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database Syst Rev. 2005;(3): CD004655. Update in: Cochrane Database Syst Rev. 2018;3:CD004655.
8. Bensky MJ, Ayalon-Dangur I, Ayalon-Dangur R. Naamany E, Gafter-Gvili A, Korcn G. Comparison of sublingual vs. intramuscular administration of vitamin B 12 for the treatment of patients with vitamin B 12 defıciency. Drug DelivTransı Res. 2019:9(3):625-630.
9. 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):721–725.
10. 10. Verma D, Chandra J, Kumar P, et al. Efficacy of oral Methylcobalamin in treatment of vitamin B 12 deficiency anemia in children. Pediatr Blood Cancer. 2017;64(12): 1-4.
11. Kartal TA, Mutlu ÇZ. Comparison of Sublingual and Intramuscular Administration Of Vitamin B 12 for the Treatment of Vitamin B 12 Deficiency in Children. Rev Invest Clin. 2020;72(6):380-385.
12. Kiliç BO, Kiliç S, Eroğlu EŞ, Gül E, Apak FBB. Sublingual methylcobalamin treatment is as effective as intramuscular and peroral cyanocobalamin in children age 0–3 years, Hematology. 2021; 26:1013-1017.
13. Varkal MA, Karabocuoglu M. Efficiency of the sublingual route in treating B I 2 deficiency in infants. Int J Vitam Nutr Res. 2021 Aug 25. DOI: 10.1024/0300-9831/a000724.

Cite as: Cakmak HM, Bildirici Y. The Efficacy, Dose and Interval Of Sublingual Methylcobalamin Spray in Children: A Single-Center Experience. Eskisehir Med J. 2022;3(3):259-63.