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Oral Methylcobalamin Treatment Effectiveness of Newborn with Vitamin B12 Deficiency

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Introduction: Vitamin B12 (Vit-B12) levels between the mothers and their infants in a neonatology unit were investigated and the effectiveness of oral methylcobalamin treatment in neonatal Vit-B12 deficiency was evaluated.
Materials and Methods: Eighty patients born between July 2018 and April 2020 at 34–42 weeks of gestation and who were found to have Vit-B12 deficiency were included in this cross-sectional study. Oral methylcobalamin was given to 40 patients, and 40 patients were followed up. Vit-B12 level and blood gas were measured in the umbilical cord blood of the infants, and a complete blood count was performed on the first day. Vit-B12 levels of the mothers were assessed. Complete blood count and Vit-B12 level were measured on the postnatal 30th day in patients who were followed up without treatment and 5 days after treatment in patients who received oral methylcobalamin treatment for 1 month.
Results: In the treatment group, the mean umbilical cord Vit-B12 level was 155.5 (±29.1) pg/ml, and the mean Vit-B12 level of the mothers was 158.8 (±57.6) pg/ml. The mean follow-up Vit-B12 level was 801.8 (±394.7) pg/ml. In the untreated group, the mean umbilical cord Vit-B12 level was 159.3 (±34.1) pg/ml, and the mean Vit-B12 level in mothers was 146.2 (±49.7) pg/ml. The mean follow-up Vit-B12 level was 189.2 (±57.6) pg/ml.
Conclusion: There was a positive correlation between umbilical cord Vit-B12 and mothers' Vit-B12 levels. Oral methylcobalamin treatment was found to be effective and safe in Vit-B12 deficiency.
Keywords: Maternal, newborn, vitamin B12 deficiency, methylcobalamin, umbilical cord

Introduction

Vitamin B12 (Vit-B12) or cobalamin deficiency is a worldwide problem in developing countries where deficiency is common in all age groups (1). Vit-B12 is a water-soluble vitamin that is only present in foods of animal origin such as meat, eggs, fish, and dairy products. Vit-B12 cannot be synthesized in the human body and is essential for growth and development in humans; therefore, Vit-B12 must be supplied by the diet. Vit-B12 is an essential vitamin B that plays a crucial role in DNA synthesis, methylation, mitochondrial metabolism, and maintenance of genomic stability (2). The most important reason for infant Vit-B12 deficiency is maternal Vit-B12 deficiency (3-5). Maternal

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micronutrient status during pregnancy impacts fetal brain development. In Vit-B12 deficiency, the onset and severity of symptoms differ according to age. In infants, neurological impairment with hypotonia, tremors, irritability, seizures, developmental delay, and cerebral atrophy is typical, and the damage is believed to occur during the first 6 months, which is a critical period for the maturation of oligodendrocytes and brain myelination. Early detection and intervention are essential to prevent irreversible neurological damage caused by prolonged Vit-B12 deficiency (6). Vit-B12 deficiency is treated with parenteral therapy. Intramuscular (IM) injections are uncomfortable in infants and also painful, expensive, and prone to complications. Despite availability, Vit-B12 is rarely prescribed in the oral form mainly because of concerns about its absorption (7). Oral treatment is more relevant to children in developing countries where nutritional deficits account for clinical Vit-B12 deficiency in most cases. Replacement suffices in nearly all cases, making oral regimen more acceptable and cost-effective (8).

In this study, our first aim was to evaluate the Vit-B12 levels between the mothers and their infants who presented to our neonatology unit. Our second aim was to study the efficacy of orally administered Vit-B12 in the treatment for Vit-B12 deficiency in newborns. Besides, we investigated whether Vit-B12 levels increased over time in newborns with Vit-B12 deficiency due to maternal causes.

Materials and Methods

Newborns born between July 2018 and April 2020 at 34–42 weeks of gestation who were found to have Vit-B12 deficiency in the umbilical cord blood were included. The patients' gestational age, gender, Apgar scores at the 1st and 5th minutes, birth weight, birth head circumference, mode of delivery, maternal age, number of pregnancies, as well as the presence of hypotonia and convulsions were examined. Patients with persistent diarrhea syndromic apperance and congenital anomaly, as well as deliveries before 34 weeks of gestation and those that received total parenteral nutrition and multivitamin support were excluded from the study.

Umbilical cord blood gas, Vit-B12 level, and complete blood count were measured within the first 6–24 h in the infants. Peripheral smear was evaluated in newborns with anemia. Vit B12 levels of mothers were measured in the last trimester or within the first 24h after delivery. Forty patients with Vit-B12 <200 pg/ml who were given oral methylcobalamin treatment (Group 1: treatment) and 40 patients who were followed up without treatment (Group 2: control) were included in the study. Follow-up Vit-B12 level and complete blood count were measured on postnatal 30th day in the control group and 5 days after the treatment in the group 1. Delta Vit-B12 (change in Vit-B12 level) was obtained by subtracting the umbilical cord Vit-B12 level from the Vit-B12 level at one month. Vit B12 concentrations were measured by chemiluminescence method using electrochemiluminescence immunoassay analyzer immunologic test (Roche, Cobas eE601 /602 analyzers) at our laboratory. To define Vit-B12 deficiency, we chose the cutoff value of <200 pg/ml, which is the most commonly used cutoff value, as shown by a recent review (9). In the present study, Vit-B12 levels of <100 pg/ml were accepted as a severe deficiency, <200 pg/ml as a deficiency, 200–350 pg/ml as insufficiency, and >350 pg/ml as normal (10). Oral Methylcobalamin Treatment Protocol:

Random sampling was used to determine which patients to treat among the newborns with Vit-B12 deficiency. Oral methylcobalamin at a dose of 500 µg/day (1 puff=3 drops=500 units, Ocean Methy B12 oral/sublingual spray/drop, Orzax, Istanbul, Turkey) was given orally in the form of drops to the newborns.

Statistical Analysis

SPSS 17.0 software was used for the statistical analysis. The normality distribution of the variables was examined. Media, mean and standard deviation were used in the descriptive analyses. Categorical variables were compared using the Pearson chi-squared test. Mann-Whitney-U test was used to evaluate the variables that did not exhibit normal distribution between the groups. The change in measured values was examined using the Wilcoxon. The Spearman correlation test was used to analyze the data. P-value less than 0.05 was considered statistically significant.

Results

In the treatment, 52.5% of the infants were male, 77.5% were born by cesarean section, the week of gestation was 37.2±1.9, and the mean birth weight was 2933±527 g. In the control group, 50% of the infants were male, 77.5% of them were born by cesarean section, the mean week of gestation was 37.8±1.7, and the mean birth weight was 3028±547g. There was no difference between the groups in terms of gender, birth weight, birth height, mode of delivery, birth head circumference, gestational week, Apgar scores, maternal age and number of pregnancies, umbilical cord pH, base excess, and lactate (p>0.05)(Table-1).Nearly infants in the groups were fed breast milk. The patients had no neurological signs of hrombocytopenia, Vit-B12 deficiency, leukopenia, or pancytopenia.

In the treatment group, the mean umbilical cord Vit-B12 level was 155.5 (±29.1) pg/ml, and the mean Vit-B12 level of the mothers was 158.8 (±57.6) pg/ml. The mean follow-up Vit-B12 level after treatment was 801.8 (±394.7) pg/ml. In the control group, the mean umbilical cord Vit-B12 level was 159.3 (±34.1) pg/ml, and the mean Vit-B12 level in mothers was 146.2 (±49.7) pg/ml. On postnatal 30th day, the mean follow-up Vit-B12 level was 189.2 (±57.6) pg/ml. The mean delta Vit-B12 was 646.3 (±392.6) pg/ml in the treatment group and 29.8 (±46.6) pg/ml in the control group (Figure 1).

Table 1. Characteristics of the treatment and control groups

Variables	Treatment *(n:40)*	Control *(n:40)*	P-Value
Gender *(Male/Female)*	21/19	20/20	0.82
Birth Weight *(gm)*	2933±527	3028±547	0.29
Birth Head Circumference *(cm)*	33.8±1.9	34.4±1.7	0.17
Gestational Week	37.2±1.9	37.8±1.7	0.09
Normal Delivery	9 (22.5%)	9 (22.5%)	1
Apgar at the 1st minute	7.6±1	7.5±0.57	0.59
Apgar at the 5th minute	8.5±1.1	8.5±0.6	0.95
Maternal Age	29.6±5.8	27.7±5.2	0.12
Number of pregnancies	2.6±1.4	2.5±1.5	0.7
Cord pH	7.34±0.08	7.35±0.07	0.41
Cord Base excess *(mmol/L)*	-3.95±2.9	-3.07±2.7	0.17
Cord Lactate *(mmol/L)*	3.11±1.89	2.63±1.08	0.17

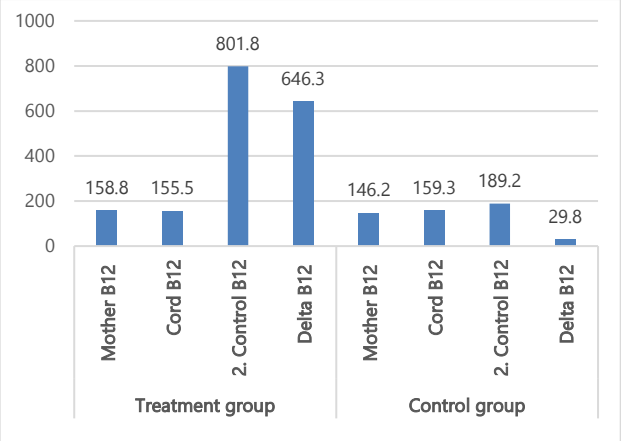


Figure 1. Vitamin B12 levels in the treatment and control

The increase in Vit-B12 and delta Vit-B12 in the treatment group was statistically significant (Table-2, Table-3) (p<0.01). In the groups, there was no significant difference in terms of leukocytes, hematocrit, thrombocyte and mean corpuscular volume (MCV) in the initial and follow-up complete blood count. Repeated analyses revealed a decrease in leukocyte, hematocrit, and MCV and an increase in thrombocyte values. In the first month when iatrogenic and physiological anemia started to develop, the decrease in hematocrit was 8.6% in the treatment group and 10.9% in the control group. In both the groups, there was a positive correlation between the umbilical cord and maternal Vit-B12 levels (group 1, r: 0.793, p=0.001; group 2, r: 0.525, p=0.03) (Table 4). In linear regression analysis, oral methylcobalamin treatment was found to increase Vit-B12 level by 613 units (0.74 fold) (Table 5).

Table 3. Changes in vitamin B12 of the groups over time

Feature	B12	Treatment *(n:40)*	Control *(n:40)*	P value
Umbilical cord B12 *(pg/ml)*	<100	2	2	1
	<200	38	38	
	200-350>	0	0	
Follow-up B12 *(pg/ml) (1st month)*	<100	0	one	<0,01
	<200	0	25	
	200-<350	one	14	
	normal	39	0	

Discussion

Newborns need 0.4 µg Vit-B12 daily, and their Vit-B12 stores are approximately 50 µg. While the ratio of daily Vit-B12 requirement with the Vit-B12 stores is 1:1000 in adults, it is 1:125 in newborns. Thus, newborns are at a greater risk of nutritional Vit-B12 deficiency later in life (11). Infants are dependent on the mother for Vit-B12 during pregnancy and breastfeeding. Vit B12 is transferred from the mother to the infant

Table 2. Changes in the hemograms and vitamin B12 levels of the groups

Variables	Treatment *(n:40)*	Control *(n:40)*	P value
Initial Leukocytes (mm^3)	15239±8810	12975±5297	0.17
Initial Hematocrit (%)	47.6±7.7	48.4±6.8	0.65
Initial MCV (femtoliter)	109.4±5.4	106.2±6.3	0.02
Initial Thrombocytes (mm^3)	288073±101042	373675±460036	0.25
Follow-up Leukocytes (mm^3)	10679±2699	9545±2573	0.12
Follow-up Hematocrit (%)	39.1±5.7	37.4±6.1	0.3
Follow-up MCV (femtoliter)	99.0±8.8	98.5±10.8	0.82
Follow-up Thrombocytes (mm^3)	393473±112058	381833±114250	0.69
Maternal Vit B12 pg/ml	158.8±57.6	146.2±49.7	0.39
Umblical Cord Vit B12 pg/ml	155.5±29.1	159.3±34.1	0.59
Follow-up Vit B12 (pg/ml) 1st month	801.8±394.7	189.2±57.6	<0.01
Delta Vit. B12 (pg/ml)	646.3±392.6	29.8±46.6	<0.01

Abbreviations. MCV: Mean Corpuscular Volum

Table 4. Relationship between the umbilical cord and maternal Vit-B12

Vitamin B_{12} *(pg/ml)*		Control	Treatment
Maternal-Umbilical cord	r	0.525	0.793
	p	0.003	0,0001

*Spearman correlation test

especially via the transplacental route and stored in sufficient quantities to meet the needs of the child during the first 6–12 months. Deficiency in the first 6 months only occurs in infants with maternal Vit-B12 deficiency (12).

In meta-analyses, low maternal Vit-B12 levels during pregnancy were found to be associated with low birth weight and preterm delivery (13). In a study by Bozkaya and Akın, Vit-B12 deficiency was observed in pregnant women, breastfeeding mothers, and in a majority of their infants (14-15). In the present study, low levels of Vit-B12 were parallel in patients with Vit-B12 deficiency and their mothers. The mean week of gestation of the groups was lower than the expected week of delivery (group 1: 37.2 weeks; group 2: 37.8 weeks).

Serum Vit-B12 levels under 350 pg/mL have been reported to be 90% sensitive for diagnosing Vit-B12 deficiency. If serum Vit-B12 level is <200 pg/ml, confirmatory diagnostic tests are not required, and empirical treatment is recommended (10,16).

Sufficient data regarding the diagnosis and treatment approach in neonatal Vit-B12 deficiency are not available. Because newborns with Vit-B12 deficiency are asymptomatic, and we observed a slight increase in follow-up Vit-B12 values in our long-term follow-up and experience, we followed the patients in group 2 closely. In this study, although Vit-B12 levels increased slightly in the control group, it was observed that they did not reach normal values (>350 pg/ml). In the tests performed 1 month later, 26 (65%) infants still had a deficiency and 14 (35%) still had insufficiency (table 3). In the patients with umbilical cord Vit-B12 level of 50 pg/ml, the follow-up Vit-B12 value reached 85 pg/ml after 1 month, but it remained below 100 pg/ml. A sufficient Vit-B12 level is essential to achieve growth and neurological maturation in the first 2 years of life from the intrauterine period. Symptoms may be overlooked because of the difficulty in evaluating neurological signs such as lethargy, apathy, infant tremor syndrome, cognitive functions, dysesthesia/ paresthesia, polyneuropathy, and depression or obscure findings in mild Vit-B12 deficiency and insufficiency in the first few months of life. Therefore, Vit-B12 deficiency should be treated even without symptoms. There is a wide range of symptoms from epileptic seizures to brain atrophy in severe cases of Vit-B12 deficiency in the infantile period. Severe neurological symptoms result from a delay in treatment. One of the most feared consequences of Vit-B12 deficiency is the development of residual insufficiency affecting 6% of neurological injuries. This may continue even after 6–12 months of treatment. Irreversibility tends to be associated with more than six months of therapeutic delay (17-18).

Oral methylcobalamin treatment in newborns with Vit-B12 deficiency: If the patient shows signs of tissue hypoxia and/or severe anemia that causes heart failure, an erythrocyte suspension is given. The Turkish hematology association recommends a protocol of 250–1000 µg/day for an average period of 4 months for oral treatment, during which the dose is gradually decreased (19). It has been reported that 2% of 500 µg oral cobalamin is absorbed from the intestines in adults with normal intestinal absorption (17). In our unit, an oral 500

μg/day methylcobalamin treatment protocol is applied for patients with Vit-B12 deficiency in the neonatal period, and whether the treatment should be continued is decided according to the repeated monthly Vit-B12 measurement results. After administration of oral methyl cobalamin treatment for 1 month, follow-up Vit-B12 values showed sufficient increase, except for one patient with inadequate treatment compliance (umbilical cord Vit-B12: 125.6 pg/ml, follow-up Vit-B12: 333.4 pg/ml). After applying the same treatment protocol regularly for a month in the patient with inadequate treatment compliance, the Vit-B12 value increased to 728.3 pg/ml. Oral methyl cobalamin treatment was well tolerated with no adverse effects in all infants.

According to the results of a meta-analysis from the Cochrane Library, the effects of oral and IM treatment on increasing serum Vit-B12 levels were found to be similar (18). Bahadır et al. showed that the treatment protocol of an oral dose of 1000 μg Vit-B12 (cyanocobalamin) applied in 48 children was effective in achieving normal Vit-B12 levels in all children (20). Sezer et al. showed that the mean serum Vit-B12 level increased from 182±47.6 pg/ml to 482±318 pg/ml after 1 month of oral treatment with 1000 μg Vit-B12 (cyanocobalamin) in 79 children with Vit-B12 deficiency. Oral cyanocobalamin is effective in treating children with Vit-B12 deficiency (21).

Strong et al. found 1000μg sublingual methyl cobalamin treatment to be equivalent to IM treatment in adults (22). Verma et al. showed that oral methylcobalamin (500μg; 30 mcg/kg /day) treatment for 1 month was sufficient in 28 children with Vit-B12 deficiency anemia aged between 6 months and 18 years (8). In the present study, mean values of Vit-B12 increased 5.15 times with oral methylcobalamin treatment, but this rate was 0.18 times in patients who were followed up without treatment.

In the present study, decreased leukocyte, hematocrit, MCV and increased thrombocyte values were observed in the follow-up complete blood count in the groups. Elevated MCV is normal in newborns at birth. Following birth, there is iatrogenic/physiological decrease in MCV and hematocrit values. The fall in hematocrit was lower in the group given vitamin B12 treatment, but there was no statistically significant difference in the groups. Megaloblastic anemia associated with Vit-B12 deficiency was absent in the groups.

The strength of the study is that it is the first study in neonates on the follow-up and treatment of Vit-B12 deficiency. The limitation of the study is that it does not include long-term neurological and laboratory follow-up results of the groups. We could not compare our results with the literature because of the unavailability of a sufficient number of studies on the newborns and early infantile period (first 4–6 months).

Conclusion

The study supports Vit-B12 supplementation during pregnancy is insufficient in developing countries. The umbilical cord Vit-B12 reflect the mothers' Vit-B12 levels. When newborns with umbilical cord Vit-B12 deficiency are not treated, adequate improvement in Vit-B12 level does not occur during their follow-up. Oral methylcobalamin treatment is well tolerated by newborns and provides effective and safe results. In newborns and infants diagnosed with Vit-B12 deficiency, especially taking into account the rapid neurological maturation process, Vit-B12 should be increased to

sufficient levels and repeated measurements should be conducted at certain intervals in the asymptomatic and/or presymptomatic period.

Conflict of Interests

The authors declare no conflict of interest related to this work.

Ethical Statement

Approval was received from the Namık Kemal University Human Clinical Research Ethics Committee (protocol number: 2020.72.03.2).

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