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BRIEF REPORT

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Efficacy of oral methylcobalamin in treatment of vitamin B12 deficiency anemia in children

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Abstract

To demonstrate the efficacy of oral methylcobalamin in treating vitamin B12 (vitB12) deficiency anemia, our prospective observational study enrolled 28 children with both macrocytic anemia and low holotranscobalamin (HoloTC) levels. Their hematological and biochemical parameters pre- and posttreatment at 1 month were compared. Hemoglobin showed mean increase of 2.89 g/dl ($P < 0.001$), rising above 10 g/dl in 24 patients (85.7%). Reticulocytes peaked at 1 week. Mean fall in mean corpuscular volume of 24.83 fl ($P < 0.001$) and mean improvement in platelets of 122,100/μl ($P = 0.001$) were noted, and mean rise in HoloTC and vitB12 were 111.36 pmol/l ($P < 0.001$) and 918.34 pg/ml ($P < 0.001$), respectively. Thus, initial responses to oral methylcobalamin in children with vitB12 deficiency anemia were adequate.

KEYWORDS

anemia, children, cobalamin, holotranscobalamin, homocysteine, megaloblastic anemia, methylcobalamin, vitamin B12

1 | INTRODUCTION

Vitamin B12 (vitB12) and folic acid (FA) deficiency results in asynchrony of nuclear and cytoplasmic maturation in hematopoietic stem cells, thus causing megaloblastic anemia (MA).[1] Over the past two to three decades, vitB12 deficiency has emerged as a more significant cause of MA, and this deficiency also affects the central and peripheral nervous systems because of its role in myelination. An early diagnosis and prompt treatment are thus essential to reverse hematological and neurological dysfunction.

Diagnosing vitB12 deficiency was previously considered straightforward with tests, such as vitB12, methylmalonic acid (MMA), and homocysteine (Hcy) levels. With the development of newer tests, subclinical deficiency states are being recognized. Holotranscobalamin (HoloTC) is the metabolically active vitB12 fraction and is released from enterocytes into portal blood for storage or into plasma for tissue usage. Because of its short half-life and ability to enter all cells, holoTC is currently believed to be a sensitive and earliest biomarker of circulating vitB12 levels.[2,3]

Conventionally, vitB12 deficiency is treated parenterally. However, several recent case series and controlled studies in adults[4–6] and fewer studies in children[7–9] have demonstrated the efficacy of oral regimens. Oral treatment is more relevant to children in developing countries where nutritional deficits account for clinical vitB12 deficiency in most cases.[10] Thus, replacement suffices in almost all cases, making an oral regimen more acceptable and cost effective.[11,12]

The objective of this study was to assess the hematological and biochemical response to oral methylcobalamin therapy among children with vitB12 deficiency anemia.

2 | METHODS

This prospective observational study was conducted at the Department of Pediatrics, Lady Hardinge Medical College, New Delhi.

Inclusion criteria were as follows: (1) age of 6 months–18 years, (2) anemia with macrocytosis,[13,14] and (3) deficient vitB12 status (defined as holoTC levels < 35 pmol/l).[15] Exclusion criteria were as follows: (1) critical illness, (2) low ferritin,[16] (3) low FA,[17] (4) proton pump inhibitor usage for >2 weeks, (5) known renal disease, and (6) history of recent blood transfusion (within last 4 weeks) or hematinic use.

Children with anemia[13] from outpatient clinics or wards were screened for macrocytosis,[14] and the children who were positive were further screened for inclusion after consent was obtained. The results from a detailed history and physical examination were

Abbreviations: CBC, complete blood count; FA, folic acid; Hb, hemoglobin; Hcy, homocysteine; HoloTC, holotranscobalamin; MA, megaloblastic anemia; MCV, mean corpuscular volume; MMA, methylmalonic acid; PS, peripheral smear; vitB12, vitamin B12

TABLE 1 Trend of change in mean values of various hematological parameters during treatment

Parameters		Mean ± SD	*P*-value (vs. day 0)	*P*-value (vs. day 7)
Hb (g/dl)	Day 0	7.94 ± 1.74	–	–
	Day 7	9.37 ± 1.50	<0.001**	–
	Day 31	10.83 ± 1.25	<0.001**	<0.001**
MCV (fl)	Day 0	109.35 ± 10	–	–
	Day 7	99.81 ± 9.27	<0.001**	–
	Day 31	84.52 ± 8.60	<0.001**	<0.001**
ARC (/μl)	Day 0	75,100 ± 86,600	–	–
	Day 7	155,600 ± 97,200	0.002*	–
	Day 31	45,900 ± 26,000	0.052	<0.001**
Platelets (/μl)	Day 0	196,100 ± 195,000	–	–
	Day 7	374,800 ± 189,900	<0.001**	–
	Day 31	318,200 ± 118,700	0.001*	0.066

**Highly significant ($P < 0.001$); *significant ($P < 0.05$).

recorded. Then, participants underwent the following baseline investigations: complete blood count (CBC) with peripheral smear (PS), serum ferritin, FA, holoTC, vitB12, and fasting Hcy levels. Supplementary Table S1 shows the various methods used for analyzing all these parameters.

Patients with low holoTC levels were included after exclusion criteria were ruled out. The patients were started on oral treatment with 500-μg tablet of methylcobalamin (Tab Nurokind, procured from M/S Mankind Pharma Ltd., India) once daily at a dosage of 30 μg/kg/day rounded to the nearest 10 μg because a liquid preparation was not available. During the treatment, patients were followed up twice: after 1 week and 1 month. At 1-week follow-up, only CBC with PS was repeated. At 1-month follow-up, levels of holoTC, vitB12, and Hcy were obtained along with CBC and PS.

Information was entered into a spread sheet using Microsoft Excel software. Statistical analysis was performed using SPSS version 15.0 software. Data were compiled and "mean ± 2SD" was calculated for all parameters studied. Continuous variables were compared using the "*t*-test" (for normally distributed data). Skewed data were analyzed using the Wilcoxon signed-rank test. Categorical data were analyzed using the chi-squared test. *P*-values < 0.05 were considered statistically significant.

The study was approved by the institutional ethics committee for human research.

3 | RESULTS

Of the 67 children with macrocytic anemia who were screened for inclusion, 28 were included for the final analysis. The others were excluded for various reasons, as shown in Supplementary Figure S1.

The clinical features at enrolment are shown in Supplementary Table S2. The majority of our study population (46.43%) were from 6 months to 1 year old. Neurological symptoms were observed in seven (25%) patients and were resolved after therapy, whereas knuckle hyperpigmentation was the most common physical sign observed in 20 (71.43%) patients. At presentation, 10 (35.7%) children had severe anemia, while 15(53.6%) had moderate anemia.

Table 1 and Supplementary Figure S2 show highly significant statistical differences in the mean values of hemoglobin (Hb), mean corpuscular volume (MCV), absolute reticulocyte count, and platelets when comparing the values at day 0 with that of days 7 and 31. Hb showed a mean increase of 2.89 g/dl ($P < 0.001$) and increased to values exceeding 10 g/dl in 24 patients (85.7%). Reticulocytes peaked at 1 week. A mean decrease in MCV of 24.83 fl ($P < 0.001$) and a mean improvement in platelets of 122,100/μl ($P = 0.001$) were observed.

Initially, all patients had low holoTC levels, which were corrected by the treatment in 27 (96.42%) patients after 1 month. In contrast, the baseline vitB12 levels were low in 19 (67.85%) patients, and posttreatment correction was observed in all of them (100%). The baseline Hcy levels were high in 25 (89.28%) patients, and posttreatment correction was observed in 17 of 25 (68%) patients.

Table 2 and Supplementary Figure S3 show the mean increases in holoTC and vitB12 of 111.36 pmol/l ($P < 0.001$) and 918.34 pg/ml ($P < 0.001$), respectively, with a mean decrease in Hcy of 35.77 μmol/l ($P < 0.001$) at the end of 1 month.

4 | DISCUSSION

Our study demonstrates the hematological and biochemical response to oral vitB12 therapy among children. It is known that passive diffusion accounts for 1.2% of the total absorption of vitB12, and bioavailability is unaffected in patients with pernicious anemia or gastroduodenal surgical resection.[18] Thus, high doses of oral vitB12 may be able to produce adequate absorption of vitB12 even without intrinsic factor.

The response to oral therapy is described among adults as reticulocytosis peaking at 1 week, with correction of WBC, platelets, and MCV after an average of 9.5, 9.7, and 22.4 days, respectively. Hb is usually the last to improve, with values exceeding 10 g/dl within an average of 34.3 days.[19] Our children showed a similar response in all parameters.

TABLE 2 Comparison between pre- and posttreatment mean values of holoTC, vitB12, and homocysteine

Parameters	Pretreatment (day 0) Mean ± SD	Posttreatment (day 31) Mean ± SD	*P*-value
HoloTC (pmol/l)	23.76 ± 5.15	135.12 ± 81.92	<0.001
Vitamin B12 (pg/ml)	161.49 ± 102.82	1,079.83 ± 363.96	<0.001
Homocysteine (μmol/l)	46.33 ± 38.29	10.56 ± 9.81	<0.001

Hb showed a mean increase of 2.89 g/dl at 1 month ($P < 0.001$) with 24 of 28 (85.7%) patients having Hb exceeding 10 g/dl; however, this value was still lower than the age-appropriate cut-off for defining anemia in 19 (67.8%) patients, suggesting that a longer duration of therapy should be used, as in other studies.[4–7]

Hcy is increased in both FA and vitB12 deficiencies, but serum MMA is increased in vitB12 deficiency only. MMA and Hcy levels together are considered to be more sensitive biomarkers for functional vitB12 status.[20] However, these values are not specific and can also be falsely elevated in renal diseases and other conditions.[21] We carefully excluded children with concomitant FA deficiency; thus, the increased Hcy levels were attributed to vitB12 deficiency only.

Few studies among adults with different durations of oral therapy have shown an adequate response. In a study from Strasburg, after an average of 8 days of oral therapy, 17 of 20 patients normalized their serum cobalamin levels ($P < 0.01$). The increase in Hb and decrease in MCV, however, were not significant.[22] Our children showed a better response, with significant correction in all hematological parameters after 1 week of therapy (Table 1). Similar results were reported by Troilo et al.[23]

Studies comparing oral and parenteral cobalamin therapy are limited but have shown similar responses. Kuzminski et al. compared daily 2,000 μg oral dosage with parenteral therapy and showed a similar reduction in MCV and increase in hematocrit at 4 months in both groups.[4] The posttreatment MMA levels were significantly lower, and vitB12 levels were significantly higher. Bolaman et al. also concluded that the hematologic parameters and recovery patterns were similar between oral and parenteral therapy.[5]

A limited number of pediatric studies also have documented an adequate response. A study among 47 vitB12-deficient children showed an effective response with 1,000 μg oral vitB12 as intermittent therapy for 4 months.[7] A few other small studies and case reports among children also supported oral vitB12 as a treatment option, even in cases of selective vitB12 malabsorption.[8,9]

Since our study included children aged 6 months–18 years, instead of using a fixed-dose vitB12 formulation for all, we used a daily dose per unit body weight of methylcobalamin. We included only isolated vitB12 deficiency cases based on a more sensitive marker, holoTC. Children with iron and/or FA deficiency were excluded because concomitant deficiency of micronutrients is known to adversely affect the response to supplemented micronutrients. Untreated vitB12 deficiency itself has been shown to be responsible for inadequate response to iron supplementation.[24]

We used methylcobalamin form of vitB12 as it is the predominant and biologically active form of cobalamin in serum and thus is theoretically better than the other forms.[25,26] Moreover, it is the only oral preparation of cobalamin without any other added supplements that is presently available in India. Oral methylcobalamin has been used in a single study from Japan, which showed an adequate response in adults.[6]

Oral vitB12 therapy can be more economical than parenteral preparations, as supported by a recent budget impact analysis.[11] This treatment is also better accepted by patients.[12] Tolerability among our patients was assessed by recording any adverse effects and basic blood investigations at follow-up visits. During the course of treatment, no patients reported any adverse effects.

5 | CONCLUSION

The initial response to oral methylcobalamin therapy among children is prompt and adequate. However, administration of oral methylcobalamin for more than one month may be necessary to normalize Hb levels to age-appropriate quantities.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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