RESEARCH PAPER

# Parenteral vs Oral Vitamin B12 in Children With Nutritional Macrocytic Anemia: *A Randomized Controlled Trial*

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**Background:** There is limited literature in children on efficacy of different routes of vitamin B12 administration for vitamin B12 deficiency macrocytic-megaloblastic anemia.

**Objective:** To compare parenteral with oral vitamin B12 therapy in children with macrocytic-megaloblastic anemia.

**Study design:** Single-center, open-label randomized controlled trial.

**Participant:** 80 children aged 2 month-18 year with clinical and laboratory features of nutritional macrocytic anemia.

**Intervention:** All children received an initial single parenteral dose of 1000 µg vitamin B12 followed by randomization to either parenteral or oral vitamin B12 for subsequent doses. Group A was given 1000 µg intramuscular (IM) vitamin B12 (3 doses on alternate days for those aged <10 year, five doses for age >10 year), followed by monthly 1000 µg IM for the subsequent two doses. Group B was given daily oral vitamin B12 1500 µg (500 µg in <2 years age) for three months. Folic acid and iron supplementation, and relevant dietary advice were given to both groups in a similar fashion.

**Outcome:** Improvement in serum vitamin B12 levels and total hemoglobin was compared three months post-treatment.

**Result:** The median(IQR) increase in serum vitamin B12 level was significantly higher in group A [600 (389,775) vs 399 (313, 606) pg/mL; *P*= 0.016]. The median (IQR) rise of hemoglobin was also more in group A [2.7 (0.4,4.6) vs 0.5 (-0.1,1.2) g/dL; *P*=0.001].

**Conclusion:** Increase in serum vitamin B12 levels and hemoglobin was better in children with nutritional macrocytic anemia receiving parenteral as compared to oral vitamin B12.

**Keywords:** *Knuckle pigmentation, Management, Methylcobalamin*.

**Trial Registration**: CTRI/2017/07/009124 ***Published online*:** May 31, 2022; ***PII***: S097475591600427

Vitamin B12/folate deficiency is reported to contribute to more than one-third of anemia prevalence in India, and it is next to iron deficiency anemia among children aged 5-9 year, and adolescents [1]. Effective parenteral and oral therapy is available to treat vitamin B12 deficiency, but clear guidelines are lacking for children with predominant hematological manifestations, especially from our region [2,3]. Taking an injection is painful for children, costlier [4], and trained staff is needed for administration. Treatment with an oral form of vitamin B12 was reported to be as effective as parenteral therapy in adults [5]. However, vitamin B12 is rarely prescribed in the oral form, mainly because of concerns about absorption [6].

This study was done to compare the efficacy of oral vitamin B12 therapy with the standard parenteral vitamin B12 therapy in improving viamin B12 levels in children with nutritional macrocytic (megaloblastic and dimorphic) anemia, after three months of treatment.

## METHODS

It was a single-center, open-label randomized control trial from March, 2015 to June, 2016, conducted at a rural tertiary care teaching hospital. Approval was obtained from the institutional ethics committee, and the trial was registered retrospecitively with the Clinical Trials Registry of India.

*Invited Commentaries: Pages 677-80.*

In a previous study among adults [7], the standard deviation of vitamin B12 levels after four months of treatment was 165 pg/mL in parenteral and 595 pg/mL in the oral route groups. Assuming the minimum expected mean difference of vitamin B12 levels between both the groups as 250 pg/mL and considering 5% level of significance, with a power of 80% and drop out of 10%, the required sample size was calculated as 40 in each group.

Randomization of the participants was done into the two groups using WINPEPI software. Sealed opaque

brown envelopes containing the randomization code were prepared by the biostatistician. It was opened by the investigator serially, just before the treatment, once the patient was enrolled after informed written consent from parents or caregivers. We screened 100 children between 2 month to 18 year of age for their eligibility for enrolment. Inclusion criteria were clinical features of pallor, hyperpigmentation of knuckles, infantile tremor syndrome (ITS), mild icterus or giddiness with at least one of the laboratory parameters from the following: peripheral smear showing all three - macrocytic red blood cells, hypersegmented neutrophils, and thrombocytopenia; mean corpuscular volume (MCV) >110 fL [8,9]; and, vitamin B12 level (by ADVIA Centaur VB12 Assay, Seimens) <150 pg/mL [10,11]. Those patients who had received a blood transfusion or vitamin B12 therapy upto one month prior; or were found to have other diseases than nutritional anemia, were excluded. Neurological conditions other than ITS were also an exclusion criteria. Demographic details, clinical presentation, nutritional assessment, anthropometry, and baseline laboratory values of anemia workup at the time of enrolment were recorded.

After enrollment in the study, all children received an initial intramuscular or intravenous single dose of 1000 µg followed by randomization to either parenteral (group A) or oral (group B) for subsequent doses. A total of 80 patients were randomized. In parenteral group, 1000 µg of vitamin B12 were given IM (or intravenous if platelet count < $50\times10^9$/L) for three doses in children less than ten years of age, whereas a total of five doses were given to those between 10-18 year of age. Subsequently, two more doses of similar strength were repeated at the end of the first and second months of follow-up. In group B, Nurokind OD (Mankind Pharma Ltd; containing methylcobalamin 1500 µg), half tablet under two years of age and one tablet to those aged 2-18 years, was given daily for a total of 12 weeks. In both groups, the investigator gave age-appropriate dietary and nutritional advice. Tablet folic acid (5 mg) was also supplemented to all children in both the groups.

All children were followed up in pediatric outpatient department weekly for the initial 3-4 weeks, and then monthly till completing three months of treatment. After three months of the intervention, all laboratory investigations were repeated, and clinical parameters like pallor, knuckle pigmentation, tingling sensation, general well-being, mood changes, and any adverse drug reactions were assessed.

*Statistical analysis*: Analysis of the data was performed using STATA 14.2. We used Student *t* test for comparison of normally distributed variables and Mann Whitney *U* test for non-normally distributed variabls. A *P* value <0.05 was considered statistically significant. For the primary outcomes, we conducted a per protocol analysis.

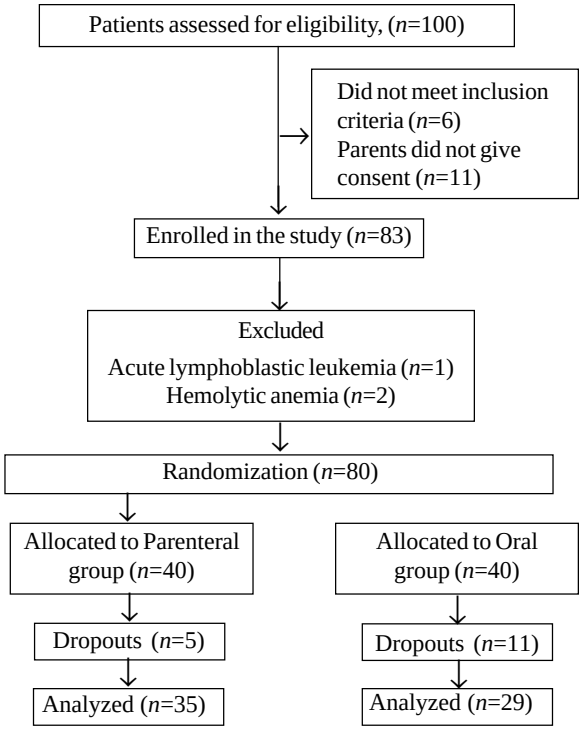


**Fig. 1** Study flow diagram.

**Table I Baseline Clinical Characteristics of Children With Nutritional Megaloblastic Anemia Enrolled in the Study**

| *Characteristics* | *Parenteral group (n=40)* | *Oral group (n=40)* |
|---|---|---|
| Age (y)[a] | 11 (2.3,15) | 13 (8,16) |
| Girls | 30 (75) | 21 (52.5) |
| *Diet type* | | |
| Vegetarian | 26 (65) | 28 (70) |
| Mixed diet | 6 (15) | 5 (12.5) |
| Only breastfeeding | 8 (20) | 7 (17.5) |
| Iron therapy[b] | 25 (62.5) | 30 (75) |
| *Nutritional status* | | |
| Normal | 21 (52.5) | 23 (57.5) |
| Undernutrition | 16 (40) | 11 (27.5) |
| Overweight | 3 (7.5) | 6 (15) |
| Pallor | 24 (60) | 26 (65) |
| *Mental changes* | | |
| Irritable | 7 (17.5) | 6 (15) |
| Apathetic | 2 (5) | 1 (2.5) |
| Tremors | 9 (22.5) | 3 (7.5) |
| Knuckle pigmentation | 37 (92.5) | 38 (95) |
| Jaundice | 6 (15) | 7 (17.5) |

*Values in no (%) or [a]median (IQR). [b]in the preceding 3 mo. All P>0.05.*

## RESULTS

Out of the 80 participants (63.7% girls), 55 (68.7%) were between 10 and 18 years of age, and 8 (10%) were infants. The flow of study participants is shown in **Fig. 1**. **Table I** shows the demographic details and baseline clinical characteristics of the participants. Majority had kunckle hyperpigmentation (75, 93.5%) and followed a vegetarian diet (54, 67.5%).

**Table II** compares the difference in laboratory values three months post-treatment in both the groups. There was a significantly higher rise in vitamin B12 level [600 (389,775) vs 399 (313,606); *P*= 0.016] and hemoglobin [2.7 (0.4,4.6) vs 0.5 (-0.1,1.2); *P*=0.001] in the parenteral treatment group (**Fig. 2**). The change in additional laboratory parameters after three months is shown in **Web Table I.**

Iron status was not studied for all the participants. However, 25 (62.5%) of patients in the parenteral treatment group and 11 (27.5%) patients in oral therapy group received additional therapeutic iron, either based on a clinical parameter or dimorphic anemia seen in the peripheral smear, which was present in 36 (45%) of the participants.

## DISCUSSION

In this single-center randomized control trial comparing oral and parenteral vitamin B12 for vitamin B12-deficiency anemia, the rise in serum vitamin B12 levels and hemoglobin was higher in the parenteral group. However, there was a statistically significant increase in serum vitamin B12 level and hemoglobin concentration after three months in both groups, suggesting that both the parenteral and oral routes effectively treat nutritional macrocytic-megaloblastic anemia in children.

A Cochrane review in 2018 [12] suggested that the oral route of vitamin B12 therapy is as effective as the parenteral group, but it had included only studies conducted in adults [7,13,14]. Only three studies were published subsequently comparing oral vitamin B12

**Table II Comparison of Pre- and Post-treatment Difference in Laboratory Values After Vitamin B12 in Children With Nutritional Megaloblastic Anemia**

| *Laboratory parameters* | *Parenteral group (n=35)* | *Oral group (n=29)* | *P value* |
|---|---|---|---|
| Change in vitamin B12 (pg/mL) | 600 (389,775) | 399 (313,606) | 0.016 |
| Change in hemoglobin (g/dL) | 2.7 (0.4,4.6) | 0.5 (-0.1,1.2) | 0.001 |
| Change in WBC ($x10^3/\mu L$) | 400 (-2500,2200) | 0 (-1450,1350) | 0.690 |
| Fall of MCV (fl) | 8.2 (1.1,18.8) | 6.1 (2.0,13.9) | 0.539 |
| Change in neutrophils (%) | -4 (-17,16) | -2 (-11,17) | 0.842 |
| Change in lymphocytes (%) | 6 (-8,20) | 8 (-5,22) | 0.895 |
| Rise in platelet count ($x10^9/L$) | -30000 (-89000,138000) | -8000 (-93000,70500) | 0.474 |

*Values in median (IQR). WBC: white blood cell, MCV: mean corpuscular volume.*

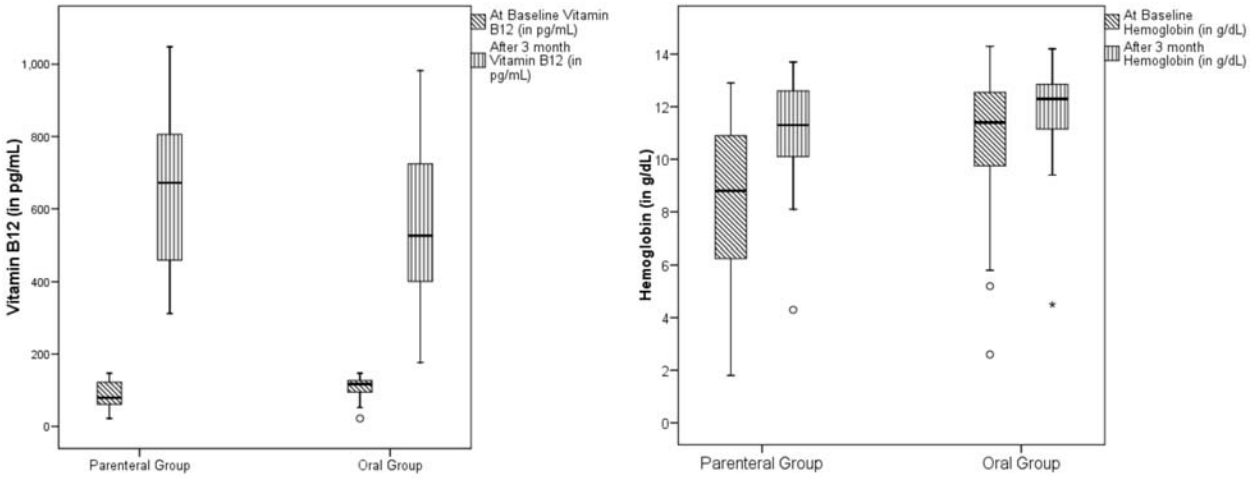


**Fig. 2** Box plots showing levels of vitamin B12 and hemoglobin: baseline and after 3 months of treatment in both groups.

**WHAT IS ALREADY KNOWN?**

- Oral route of vitamin B12 is as effective as conventional parenteral route in adults, but role of oral treatment in children with nutritional vitamin B12 deficiency remains unclear.

**WHAT THIS STUDY ADDS?**

- The rise of hemoglobin and serum vitamin B12 level were significantly higher in children given parenteral vitamin B12, as compared to those given orally.

therapy with intramuscular injections in children [15-17]. Various studies have compared different protocols for treating vitamin B12 deficiency with duration ranging from 1 week to 3 months. One of the studies had used vitamin B12 ampules in oral form for participants in the oral arm, and the other group had received multivitamin tablets [17]. Earlier studies with similar designs on adults or children with megaloblastic anemia reported similar results after 3-4 months of treatment [7,13,15]. It was noted that oral vitamin B12 therapy could be an effective alternative that reduces treatment costs [14,18,19]. However, we noted a drop out of 11 (37.5%) children in the oral arm. We cannot ensure treatment completion and cure in this loss to follow up group; though, it may be cost-saving overall.

The main limitation of our study was that we did not investigate methylmalonic acid and homocysteine levels, which are more sensitive laboratory methods for vitamin B12 deficiency. An extensive workup for iron depletion/ repletion, pernicious anemia, or other etiology was not done, unless clinically indicated. However, we supplemented iron in both groups. No subjective assessment was done for participants' mental status or satisfaction level of their parents. Vitamin B12 has a longer half-life, so long-term follow up may be necessary for finalizing an effective regimen. However, in the future, this can be expanded further, and evidence for the long-term effectiveness of oral treatment needs to be studied for confirmation of efficacy.

In conclusion, there was more increase in serum vitamin B12 levels and hemoglobin with parenteral vitamin B12 than the oral route; though, both groups showed improvement. Pediatricians should take decision about route of giving vitamin B12 after considering the efficacy data, in addition to considerations about cost, compliance and discomfort.

*Ethics clearance*: IEC, Pramukhswami Medical College; No. HREC/ HMPCMCE/2015/129, dated March 14, 2015.
*Note*: Additional material related to this study is available with the online version at *www.indianpediatrics.net*
*Contributors*: RT, JT,: literature search, Interpretation of data, drafting the article, revising it critically for important intellectual content; UP,KT: concept and design of study, acquisition of data, analysis and interpretation of data, drafting and revising it critically for important intellectual content and final approval of the version; MP: re-analyzing data and interpretation of data, revising it critically for important intellectual content. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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**Web Table I Change in Laboratory Values After Vitamin B12 in Children With Nutritional Megaloblastic Anemia**

| | *Parenteral group* | | | *Oral group* | | |
|---|---|---|---|---|---|---|
| *Variables* | *Pre-treatment (n=35)*[a] | *Post-treatment (n=35)* | *P value* | *Pre-treatment (n=29)*[a] | *Post-treatment (n=29)* | *P value* |
| Vitamin B12 (pg/mL) | 85 (61,127) | 653 (459, 835) | <0.001 | 112 (89,124) | 506 (399,726) | <0.001 |
| Hemoglobin (g/dL) | 9.4 (6.5, 11.8) | 11.3 (10.1, 12.8) | <0.001 | 11.3 (9.6, 12.7) | 12.3 (11.2, 13) | 0.007 |
| White blood cell ($x10^3/\mu L$) | 7.5 (5.05, 10.5) | 7.8 (6.5, 8.6) | 0.850 | 7.6 (5.9, 9.5) | 7.9 (7.15, 8.75) | 0.82 |
| Mean corpuscular volume (fL) | 86 (73, 97) | 75 (69, 80) | <0.001 | 84 (79,98) | 79 (73, 84) | <0.001 |
| Neutrophils (%) | 54 (34, 66) | 50 (40,60) | 0.939 | 53 (42,62) | 54 (47,65) | 0.87 |
| Lymphocytes (%) | 46 (31-57) | 38 (32, 44) | 0.043 | 44 (32, 57) | 38 (30,43) | 0.019 |
| Platelet count ($x10^3/\mu L$) | 330 (178.5, 441) | 286 (256, 346) | 0.436 | 314 (259, 410) | 324 (265, 371.5) | 0.60 |

*All values are in median (IQR).* [a]*data shown only for those who completed the study.*