INVITED COMMENTARY

Is the Time Ripe to Shift to Oral Vitamin B12 Therapy in Megaloblastic Anemia – Perhaps, Not Yet!

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Vitamin B12 (cobalamin) plays a crucial function in cellular metabolism, especially in maturation of blood cell precursors and myelination of the nervous system. It is produced by microbes and is primarily found in foods of animal origin. Intrinsic factor, produced by the stomach parietal cells, and the cubam receptor in the distal ileum are both necessary for intestinal absorption [1]. Clinical spectrum of B12 deficiency may vary from mild anemia to extreme forms of neurological deficits including ataxia, dementia, psychosis, and pancytopenia [2]. Autoimmune pernicious anemia, caused by lack of intrinsic factor production by gastric parietal cells, is the main risk factor for developing B12 insufficiency in higher-income countries. Insufficient dietary intake is the most common cause in low-income countries. In a study done by Yajnik, et al. [3], 67% of the randomly selected men had low vitamin B12 levels, most of them were middle class residents and vegetarians. The prevalence of vitamin B12 deficiency is around 47% amongst north Indian population [4].

Cobalamin deficiency demands early recognition and effective administration of therapy. For treatment of vitamin B12 deficiency, parenteral formulations are preferred due to unpredictable absorption through oral route and are given initially on daily/alternate day basis for 10 doses, then weekly for four doses and sub- sequently once a month. Even in patients with gut disease causing malabsorption, pernicious anemia or gastric resection, oral vitamin B12 therapy can still achieve reaso-nable results due to absorption via passive diffusion (1.2 percent of total absorption of vitamin B12). Though the British guidelines recommend oral supplementation for mild vitamin B12 deficiency, there are no clear recommen-dations for our population [5]. Complete correction of anemia usually takes 6-8 weeks, but reticulocytosis appears within 4-7 days with disappearance of megalo-blastic marrow changes within 48 hours. In this context, the study by Tondon, et al. [6], published in the current issue of the journal, is truly relevant for the low-income population.

In this open labeled randomized controlled study [6], 80 children with clinical and laboratory signs of nutritional macrocytic anemia, aged 2 months to 18 years, were included. All patients received first 1000 µg parenteral dose, after which they were randomly assigned to receive the following doses parenterally (group A) or orally (group B). Post 3 months of treatment, the parenteral therapy group experienced a noticeably greater increase in hemoglobin [2.7 vs 0.5; P=0.001] and vitamin B12 levels [600 vs 399; P=0.016]. This was done after matching the groups for age, sex, diet, nutritional status etc. The study is adequately powered (80%), and recruited required subjects in both arms to justify the results.

The current study [6] has efficiently compared the efficacy of therapy via both oral and parenteral routes in the Indian population but addressing a few shortcomings could have been a bonus. Folic acid and iron deficiency were not identified separately, and iron supplementation was given based on clinical parameters and laboratory evidence of dimorphic anemia. Matching for highly prevalent dual deficiency anemia and proper diagnosis of iron deficiency by serum ferritin could have been done. The reason behind giving first parenteral dose to all participants is not clear. This highlights the ethical dilemma for treating deficient patients with standard of care supplementation. With evaluation for etiology of vitamin B12 deficiency (pernicious anemia/malabsorption/ low intake etc.), the study [6] could have become more robust. This may have an important bearing on response to different therapeutic routes as well. Finally, the study [6] did not include patients with very severe anemia as the mean hemoglobin level of the parenteral group was 9.4 g/dL and the oral group was 11.3 g/dL, and it is well known that rise in hemoglobin is quicker with lower baseline level.

Kuzminski, et al. [7] randomized newly identified vitamin B12 deficient patients to vitamin B12 via intramuscular or daily oral schedule and observed better increase in serum cobalamin levels with oral therapy.

Verma, et al. [8] demonstrated a prompt and adequate biochemical response with only oral therapy in children with isolated vitamin B12 deficiency; however, it took more than a month for the hemoglobin to improve.

Supplementation through oral route is always preferred by the patients solely because of the ease and avoidance of painful injection. Cobalamin injections can be associated with injection site reactions, nausea, gastrointestinal disturbances, and precipitation of hypokalemia. According to a budget impact research, oral vitamin B12 therapy can be more affordable than parenteral preparations [9]. On the other hand, parenteral therapy has its own advantage of producing quick response and efficiency in patients with severe malabsorption problems, and cases where compliance is an issue.

The debate is ongoing regarding the route of cobalamin therapy. More randomized studies like this are needed in future, taking care to include isolated vitamin B12 deficiency cases, different food habits, complete etiological work up as well as a longer follow up.

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