Comparative Analysis of Oral and Parenteral Routes of Vitamin B12 Administration

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Abstract

Vitamin B12 is essential for the neurological system, and erythropoiesis among other important functions. Malnutrition, malabsorption such as in a case of atrophic gastritis and certain drugs like Metformin, can cause B12 deficiency. B12 can be administered both orally and parenterally. The rout of administration of B12 has been subject to extensive research regarding efficacy.

The focus of this review was to investigate whether one route of administration is superior to the other. Only randomized trials were included and studies about B12 administration for purposes other than pure deficiency, were excluded. Three studies were included. In conclusion, the published data suggested that oral and parenteral both are equally efficient with little controversy. Further research with better study design and larger sample size is mandatory.

Keywords: Vitamin B12 administration, Oral, parenteral

Introduction

A collection of nutrients called vitamins are necessary for a healthy human metabolism. Human growth, the maintenance of the neurological system, and synthesis of RBCs all require vitamin B12 also known as cobalamin. Items including eggs, seafood and meats are the only natural providers of vitamin B12. Age-related daily needs dictate the recommended dietary allowances. RDA for adults is 2.4 µg /day of vitamin B12 as stated by Doets EL, in 't Veld PH, Szczecińska A (1). Age-related increases in vitamin B12 insufficiency are likely brought on by the increased likelihood of food-cobalamin malabsorption in this population. In addition to chronic H. Pylori infection, chronic metformin, proton pump inhibitor usage, and gastric atrophy is known to be the main cause of this malabsorption (2).

Individuals in a lower strata of society, females, and non-Hispanic Blacks are more prone to have poor vitamin B12 consumption, according to an examination of NHANES data from 2015–2016 (3). In the USA and the United Kingdom, the frequency of vitamin B12 insufficiency is approximately 20% in persons over 60 compared to roughly 6% in adults under 60. Additionally, during pregnancy, blood vitamin B12 levels frequently decrease, occasionally to subnormal levels, although they typically rebound to normal following delivery (4). Historically, intramuscular injections have been used to deliver vitamin B12 supplementation. However, a number of case-control and case series research have recently shown that oral intake after delivery has an equivalent level of effectiveness and safety (5). Although vitamin B12 is widely accessible and has a proven safety record, oral prescriptions for it are uncommon. But in Sweden in 2000, 73% of the entire amount of vitamin B12 prescription was taken orally (6). A single-center, randomized control trial was carried out recently, which concluded that parenteral vitamin B12 increased hemoglobin values and serum levels better than the oral intake, however, both groups revealed increased levels (7).

There was a systematic review conducted in 2015 and then updated in 2018. Vitamin B12 therapy by oral versus intramuscular injection was contrasted in two randomized control studies. B12 was administered orally at doses of 1,000 and 2,000 mcg. Both trials used a 1,000 mcg intramuscular vitamin B12 dosage, which was given by nurses. According to the scant evidence found in this systematic analysis, daily high dosages of 2000 mcg of vitamin B12 taken orally are just as beneficial as injections into the muscles (8). The trials that were examined also provided scant evidence for certain individuals with disorders linked to malabsorption receiving sufficient hematological, biochemical, and clinical effects of per oral B12 supplementation.

Objectives

To determine the efficacy of oral vitamin B12 compared to parenteral vitamin B12 for vitamin B12 deficiency.

What makes this review significant?

There was a review conducted by Vidall J, Butler CC, Cannings R et al in 2005 (8), where they concluded that in persons who are vitamin B12 deficient, large oral dosages of the vitamin may be just as effective as parenteral vitamin B12 delivery in achieving brief hematological and nervous system outcomes. In 2018, there was an update of this review by Wang H et al, where it was demonstrated that oral therapy is cost effective and IM and oral vitamin B12 have similar effects for restoring normal blood vitamin B12 levels(9). They signified that vitamin B12 taken orally has lower risks than parenteral Vitamin B12. Better randomization along with effective blinding procedures and a larger participant pool along with proper reporting should all be used in subsequent research studies.

Methods and Material

Study selection criteria for the current systematic review:

- The inclusion criteria for our systematic review were randomized trials assessing the efficacy of oral versus parenteral routes of Vit B12 administration.
- Exclusion criteria included patients with any confounding diseases like end-stage renal failure and research with the objectives of Vit B12 administration for cardiovascular diseases.

Population type

Vitamin B12 deficient participants who satisfied the requirements for vitamin B12 replacement treatment because they are vitamin B12 deficient.

Criteria for diagnosing vitamin B12 insufficiency

Vitamin B12 insufficiency levels were defined as serum levels below 200 pg/mL (below 148 pmol/L).

Intervention used:

Oral administration of Vit B12 to 1 group and parenteral to other.

Outcome measurements:

Comparison of efficacy of both routes of administration, with other considerations such as future direction and socioeconomic effects. The following results were examined in the review, but they were not used to select which research to include or retain.

Data collection and analysis

We looked through all possibly relevant publications' complete texts. We retrieved important participant and intervention variables as well as trial results for those studies that met the inclusion criteria. We incorporated important trial features such as trial design, site, and sample size population. In order to reduce the chance of bias, we explained the procedure used to create the selection sequence for each included experiment. When studies' inclusion criteria, settings, treatments, and follow up protocols were sufficiently comparable, random effects meta-analyses was conducted taking into account the impacts of the whole distribution (10).

Description of Studies

Characteristics of included studies:

Rahul Tandon 2022

Methods	Single-centered, open-label randomized control trial (March 2015 - June 2016)
Participants	**Inclusion criteria:** • Age less than 18, • Mean corpuscular volume (MCV) above 110 fL, hyper-segmented neutrophils present, thrombocytopenia • Vitamin B12 levels below 150 pg/ml. **Exclusion criteria:** Blood transfusions or Vit B12 therapy prior
Interventions	Study centers: 1 Prior treatment: No
Aim of study	To compare oral vitamin B12 therapy with parenteral therapy in children with macrocytic-megaloblastic anemia. **Copied from research paper**

Random sequence generation (selection bias)	WINPEPI software
Blinding of participants and personnel	Open-label study

Zahit Bolaman 2003

Zahit Bolaman 2003

Methods	A ninety day, single-centered, prospective, randomized, open-label study,
Participants	**Inclusion criteria:** aged ≥16 years • serum vitamin B12 concentration <160 pg/ml • megaloblastic anemia MCV >94 fL (normal value, 80–94 fL). **Exclusion criteria:** Cancer history, lack of folate, inability to take oral medicine, and medication use
Interventions	Number of study centers: 1 Treatment before study: No
Aim of study	To assess the effects and financial cost of oral versus intramuscular vitamin B12 treatment in patients with megaloblastic anemia due to cobalamin deficiency
Random sequence generation (selection bias)	Block randomization method
Blinding of participants and personnel	The open-label study, single center

Rabia Gönül Sezer 2018

Methods	Jan to Dec 2016, prospective, randomized, single-center
Participants	**Inclusion criteria:** Children aged 1 month to 18 years with serum vitamin b12 levels below 300 pg/ml, focusing on symptoms like failure to thrive, anemia, and tingling sensation. **Exclusion criteria:** It excluded newborns with no signs of failure to thrive or anemia and patients with chronic diseases, those allergic to vitamin B12, and individuals receiving micronutrients supplementation or lacking consent.
Interventions	Number of study centers: 1 Treatment prior to study: No
Aim of study	To compare the efficacy of oral vitamin B12 formulations and intramuscular vitamin B12 in restoring serum B12 levels in children with nutritional vitamin B12 deficiency.
Random sequence generation (selection bias)	Not mentioned in research article

Interventions

All of the trials included in this group compared oral Vit B12 with the parenteral administrations.

Regarding Study, no 1 of included research; All individuals who entered the trial received a single 1000 g intramuscular or intravenous dosage; afterwards they were randomly allocated to receive the following doses parenterally (group A) or orally (group B).

In the parenteral group, children under the age of ten received 03 doses of 1000 g of vitamin B12 administered intramuscularly (IM), whereas children aged ten to eighteen received a total of 05 doses. Afterwards, two further doses of a comparable potency were administered again in the end of the first and second follow-up months.

In group B, daily doses of 1500 g for children under two and one pill for those between two and 18 years old were administered for a total of 12 weeks.

Regarding Study, no 2 Cobalamin 1000-g was given intravenously to the parenteral group once a day for 10 days. After 10 days, both treatments were given once a week for 4 weeks, and subsequently once per month for the rest of their life.

The 1000-g ampule of Vit B12 was combined with 20 milliliter of fruit juice and supplied orally once daily for 10 days to the per oral group. Because cobalamin pills weren't accessible in Turkey at the time of this trial, they weren't used. At trial days 0, 10, and 30 of therapy, the same doctor spoke with and evaluated each patient.

Regarding the Study, no 3, parenteral treatment protocol included one week at 100 mcg per day, followed by one week at 1000 mcg on alternate days, one week at 1000 mcg twice per week, and one week at 1000 mcg. The oral dose comprised a mixture of a multivitamin complex including 50 mg thiamin, 250 mg pyridoxin, and 1000 vitamin B12 as part of their treatment. Patients were given one pill daily for a month, at least an hour before a meal when they were fasting.

Outcomes

Endpoints quoted in the abstract of publications

Study No. 1	Outcome measures written in the abstract: Three months after therapy, changes in blood vitamin B12 levels and total hemoglobin levels were compared.
Study No. 2	Not mentioned in the abstract
Study No. 3	Not mentioned in the abstract

Trials reporting our primary outcomes:
All of the trials included in this review reported the serum levels of Vit B12 and other hematological parameters before and after the administration of treatment doses.

Study No 1 reported that when compared to children who received vitamin B12 orally, those who received parenteral vitamin B12 saw a substantial increase in hemoglobin and blood vitamin B12 levels.

Study No. 2 in this systematic review, therapy with oral vitamin B12 was just as efficient as therapy with IM cobalamin. In addition, oral vitamin B12 had lower cost and was more tolerated compared to intramuscular therapy. To ascertain the efficacy of oral vitamin B12, longer term investigations are required due to the smaller sample size and short duration of this study.

As per study no. 3 values for vitamin B12 after therapy were substantially higher than those before treatment. Vitamin B12 levels rose in the parenteral administration arm from 183.5 ± 47 pg/mL to 482 ± 318.9 pg/mL in the oral and from 175.5 ± 42.5 pg/mL to 838 ± 547 pg/mL in the parenteral treatment arm.

Regarding future directions, they suggested that as a first-line therapy for vitamin B12 insufficiency in children, oral preparations may be deemed safe.

Primary outcome:
Serum Vit B12 values were significantly increased in all three studies but were different for oral and parenteral groups.

The study conducted by Rahul Tandon et al revealed that there was a considerably higher increase in vitamin B12 level in the parenteral group [600 (389,775) vs 399 (313,606) pg/ml. Eighty participants (63.7%) were girls, 55 (68.7%) were between the ages of 10 and 18, and eight (10%) were young children. **So the Vit b12 level increased in the parenteral group more than oral.**

In research performed by Zahit Bolaman et al 10 of the 70 patients who were included in the trial were eliminated because they did not show up for the follow-up visit after the first 10 days of therapy. On day 0 (zero) serum levels of Vit B12 were 72.9 in the oral group with SD (54.8), while 70. 2 in the parenteral group with SD (59.1). After 90 days of treatment a rise in serum levels was noticed, 213.8 in the oral group while 225.5 in the parenteral group. **They concluded that both routes of dosage application were equally effective.**

In Rabia Gönül Sezer et al's prospective research, 142 children (66 girls and 76 boys) were included. Of those, 60 received intramuscular treatment and 82 received per oral vitamin B12 therapy. Vitamin B12 levels rose in the oral intervention group from 183.5 47 pg/mL to 482 318.9 pg/mL and in the injectable medication arm from 175.5 42.5 pg/mL to 838 547 pg/mL. **They concluded that both routes are effective but the parenteral group showed a slight extra rise in serum Vit B12 levels than the other group.**

Discussion

Doctors frequently believe that taking oral supplements would lead to an increase in the well-being and quality of life of vitamin B12 deficient patients. But their protocols are not evidence-based (11). Over time, doctors have grown more confident in oral vitamin B12.

There was a study conducted in Sweden; its objective was to assess the patterns of VitB12 sales in the market. They experienced that oral doses were registered not only for short-term outcomes but also for maintenance purposes (12). Researchers also revealed that oral dose was better for some patients. After many of these cases, researchers started comparing the efficacy of oral and parenteral routes relating to their normalizing serum level effects.

In this systematic review, we included three randomized controlled trials directly related to the study objective. The follow-up duration ranged from 90 days to 12 months. We had 292 patients having vitamin B12 deficiency, participating in this research. After consideration of study participants, management, outcome measures, and follow-up, we established that meta-analysis was not appropriate. A major consideration was the variations of oral treatment regimens and varied eligibility for study inclusion.

All three studies included in this review possess the same dose of 1000mcg, with no issue with higher oral doses. Two studies concluded that with parenteral administration there was more increase in Vit B12 serum levels, while one of them concluded that both routes of administration have equal effects. Furthermore, there were also no substantial differences in Haemoglobin MCV levels and total homocysteine across the treatment groups. The expenses of management delivered in the per oral form of vitamin B12 costs were far less than in the parenteral vitamin B12 therapy group.

The majority of dietary vitamin B12 passes through the body actively through intrinsic factors, with passive diffusion accounting for around 1% of vitamin B12 absorption. As a result, an oral administration of 1000 g daily should be enough to achieve the necessary dietary daily requirement (12). All three studies were not blinded. Nevertheless, the results were determined by both the hematological and neurological outcomes of both therapies, but laboratory tests were most likely blinded.

Due to the small population size and low quality of data, we could not assess whether the lack of intrinsic factors which are crucial for absorption can affect the normalization function of oral and parenteral routes. There was a review conducted by Emmanuel Andrès et al in 2010 to evaluate oral and nasal methods other than traditional parenteral ones focusing on patients with VitB12 malabsorption. There were three prospective randomized trials and five prospective cohort studies that revealed confirmation that oral cobalamin therapy may properly address cobalamin deficiency (13).

All three studies were undertaken in primary care settings, where most persons with vitamin B12 deficiency are managed, making generalization of the results easier. Another element influencing generality is that the three studies included extensive exclusion criteria.

The research included in this review employed both methylcobalamin and cyanocobalamin. It must be mentioned that the bioavailability of cyanocobalamin in aqueous solution formulations is significantly decreased. Additionally, normalizing blood levels of vitamin B12 and its metabolites indicates therapy response is insufficient. There is the possibility of no direct relationship between blood vitamin B12 adjustments and clinical symptom relief (14). Evidence given in the current 3 studies is also insufficient because only one of them has documented the post-treatment neurological responses.

Conclusion

This debate on the efficacy of different routes of administration has a history of almost 50 years. But still, there is a gap of evidence in the literature. The published data suggests that oral and parenteral routes are equally efficient with little controversy.

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