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Is oral vitamin B12 as effective as IM vitamin B12 in treating B12 deficiency?

Dr. Khaled Amer Shen
Family Medicine. PHCC Qatar
K_shen20022002@yahoo.com
Dr. Samer Al Daher Al Khateeb
Internal Medicine. PHCC Qatar
Samerdkh1@gmail.com

Abstract:

Vitamin B12 deficiency is a common problem, we as practitioners face every day. Most patients come with vague symptoms of fatigability, low energy, and some with neurological symptoms as numbness, and rarely with psychological symptoms.

So B12 level is one of the tests we order for those symptoms and treating patients with vit B12 deficiency is a cure in those patients. Some of those patients need long term treatment with vitamin B12, so PO medication, is much more convenient, and cost effective. By reviewing different studies, we found oral B12 medication in high doses is as effective as IM vitamin B12 in treating those patients.

Key words: Cyanocobalamin, Vitamin B12, Homocysteine, intrinsic factor, megaloblastic anemia.

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الملخص:

نقص فيتامين ب12 مشكلة شائعة ، نحن كممارسين نواجها كل يوم. يعاني معظم المرضى من أعراض مبهمة كالتعب ، وقلة الحيوية ، وبعضهم يعانون من أعراض عصبية مثل الخدر ، ونادرًا ما يعانون من أعراض نفسية. لذا فإن مستوى ب12 هو أحد الاختبارات التي نطلبها لهذه الأعراض وعلاج المرضى الذين يعانون من نقص فيتامين ب12 هو علاج لهؤلاء المرضى.

يحتاج بعض هؤلاء المرضى إلى علاج طويل الأمد بفيتامين ب12 ، لذا فإن العلاج عن طريق الفم هي أكثر ملاءمة وفعالية من حيث التكلفة مقارنة بالعلاج بالحقن العضلية. وأخيراً من خلال مراجعة الدراسات المختلفة ، يمكننا أن نستنتج أنّ أدوية ب12 الفموية بجرعات عالية فعالة مثل حقن فيتامين ب12 العضلية في علاج هؤلاء المرضى.

الكلمات المفتاحية: سيانوكوبالامين ، فيتامين ب ١٢ ، الهوموسيستين ، العامل الداخلي ، فقر الدم الضخم الأرومات.

Introduction

Although the true prevalence of cobalamin (Vit B12) deficiency in the general population is unknown, it increases with age. Approximately 15% of adults older than 65 years of age have laboratory findings of vitamin B_{12} deficiency. This prevalence may be attributed to the high frequency of hypochlorhydria of 25% to 50%, which has been reported in the older adult population. The widespread use of proton pump inhibitors to control gastric secretion is becoming a contributing factor. Cobalamin deficiency is produced by any of several mechanisms that are not always exclusive of each other and involve inadequate intake and reduced absorption (Elghetany M. Tarek, Katherine I. Schexneider and Katalin Banki 2017).

As an Internal medicine specialist, General Practitioner or Family Physicians, we see many patients with low vitamin B12, some of them are symptomatic, and we always ask same question, shall we treat or not, and is it oral or parental.

After reviewing some literate, I did switch some of my patients to oral vitamin B12, as it's more convenient and more cost effective, and patients achieved same hematological and neurological results after that. So, to go through this question, let’s go through vitamin B12 in general (chemistry, sources, and metabolism).

Research problem

All individuals with documented vitamin B12 and/or folate deficiency should be treated. There are several available formulations and possible routes of administration.

Doctors are more likely to give vitamin B12 using injections into the muscle (intramuscular injection) because they may be unaware of the option to use oral vitamin B12 or uncertain about how well it works.

The treatment with oral vitamin B12 is easy for patient rather than injection.

Is oral vitamin B12 as effective as IM vitamin B12 in treating B12 deficiency?

Aim and objectives

Aim:

This s metanalysis aims to discover if oral vitamin B12 as effective as IM vitamin B12 in treating B12 deficiency

Objectives:

Compare the improvement of Vitamin B12 parameters after oral or IM Vitamin B12 treatment

Metanalysis of 3 studies using oral and IM vitamin B12

Research importance

If oral vitamin B12 as effective as IM vitamin B12 in treating B12 deficiency, it will be easy for patient to use oral vitamin B12 rather than injection, it will be convenience and cost effective.

Vitamin B12

Vitamin B12 is synthesized by certain microorganisms, and humans are ultimately dependent on animal sources. It is found in meat, fish, eggs and milk, but not in plants. Vitamin B12 is not usually destroyed by cooking. The average daily diet contains 5–30 μg of vitamin B12, of which 2–3 μg is absorbed. The average adult stores some 2– 3 mg, mainly in the liver, and it may take 2 years or more after absorptive failure before B12 deficiency develops, as the daily losses are small (1–2 μg) (Kumar P, Michael L Clark 2017).

Cardiovascular disease and B12 vitamin:

The circulating concentration of the amino acid Homocysteine is an independent risk factor for cardiovascular disease.

A high concentration is related to ischemic heart disease, stroke, thrombosis, pulmonary embolism, coronary artery stenosis, and heart failure. The strength of the association is similar to smoking or hyperlipidemia.

Proposed mechanisms, based on experimental evidence, by which Homocysteine detrimentally affects vascular function, include:

- the direct damaging effects of homocysteine on endothelial cells of blood vessels
- an increase in blood vessel stiffness
- an increase in blood coagulation.

Homocysteine is not found in food but results from metabolism within the body which depends on folic acid, vitamin B12 and pyridoxine (vitamin B6). Deficiency of one or more of these vitamins is common in the elderly, which would increase the concentration of homocysteine. If an elevated homocysteine concentration was causally linked to cardiovascular disease, then it should be possible to lower the risk by administering one or more of these vitamins to lower the homocysteine concentration. Some recent studies, however, suggest that lowering homocysteine concentrations in this way does not reduce the risks of cardiovascular disease (Kumar P, Michael L Clark٢٠١٢)

B12 Absorption:

The absorption of vitamin B_{12} in humans is complex. Vitamin B_{12} in food is bound to proteins and is released from the proteins by the action of a high concentration of hydrochloric acid present in the stomach. This process results in the free form of the vitamin, which is immediately bound to a mixture of glycoproteins secreted by the stomach and salivary glands. These glycoproteins, called R-binders (or haptocorrins), protect vitamin B_{12} from chemical denaturation in the stomach. The stomach's parietal cells, which secrete hydrochloric acid, also secrete a glycoprotein called intrinsic factor. Intrinsic factor binds vitamin B_{12} and ultimately enables its active absorption. Although the formation of the vitamin B_{12} - intrinsic factor complex was initially thought to happen in the stomach, it is now clear that this is not the case. At an acidic pH the affinity of the intrinsic factor for vitamin B_{12} is low whereas its affinity for the R-binders is high.

When the contents of the stomach enter the duodenum, the R-binders become partly digested by the pancreatic proteases, which causes them to release their vitamin B_{12}. Because the pH in the duodenum is more neutral than that in the stomach, the intrinsic factor has a high binding affinity to vitamin B_{12}, and it quickly binds the vitamin as it is released from the R-binders. The vitamin B_{12}-intrinsic factor complex then proceeds to the lower end of the small intestine, where it is absorbed by phagocytosis by specific ileal receptors (Weir, D.G. & Scott, J.M. 1999).

Causes of Vit B12 Deficiency:

There are a number of potential causes of vitamin B12 deficiency, reflecting the relatively complex absorption process described above and numerous potential sources of interference with this process. The most common of these are pernicious anemia, an autoimmune condition, and nonimmune disorders of the stomach or small intestine that interfere with vitamin B12 absorption (eg, bariatric or intestinal surgery).

Older individuals may have a combination of conditions that interfere with absorption of vitamin B12 from food, including gastric atrophy, achlorhydria due to proton pump inhibitor, intestinal bacterial overgrowth due to antibiotics, and/or excess alcohol. These individuals can adequately absorb crystalline vitamin B12 from supplements; thus, this condition is referred to as food cobalamin malabsorption. A similar phenomenon was reported in individuals infected with human immunodeficiency virus (HIV) (Means R. T & Fairfield K. M. 2019).

Clinical Features of B12 Deficiency:

The onset is insidious, with progressively increasing symptoms of anemia. Patients are sometimes said to have a lemon-yellow color owing to a combination of pallor and mild jaundice caused by excess breakdown of hemoglobin

A red sore tongue (glossitis) and angular stomatitis are sometimes present.

The neurological changes, if left untreated for a long time, can be irreversible. These neurological abnormalities occur only with very low levels of serum B12 (less than 60 ng/L or 50 pmol/L) and occasionally occur in patients who are not clinically anemic. The classical neurological features are those of a polyneuropathy progressively involving the peripheral nerves and the posterior and eventually the lateral columns of the spinal cord (subacute combined degeneration). Patients present with symmetrical paresthesia in the fingers and toes, early loss of vibration sense and proprioception,

and progressive weakness and ataxia. Paraplegia may result. Dementia, psychiatric problems, hallucinations, delusions, and optic atrophy may occur from vitamin B12 deficiency (Means R. T & Fairfield K. M 2020).

Investigation:

we are not going to talk about all tests needed to be done, but we will talk about most important tests.

- CBC: as it may show Megaloblastic anemia, with high MCV more than 96, as we have large immature RBC with nuclei.
- LFT: it may show high Bilirubin, due to increase destruction of immature RBC.
- serum B12.
- absorption test (it's not essential in all cases): the test called Schilling test (Means R. T & Fairfield K. M. 2020).

Studies comparing using oral and IM vitamin B12:

1) **Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency: a systematic review of randomized controlled trials**: Butler CC, Vidal-Alaball J, Cannings-John R, McCaddon A, Hood K, Papaioannou A, Mcdowell I, Goringe A (2006).

A systematic review was conducted searching databases for relevant RCTs. Outcomes included levels of serum vitamin B(12), total serum homocysteine and methylmalonic acid, haemoglobin and signs and symptoms of vitamin B(12) deficiency.

Two RCTs comparing oral with intramuscular administration of vitamin B(12) met the inclusion criteria. The trials recruited a total of 108 participants and followed up 93 of these from 90 days to 4 months. In one of the studies, mean serum vitamin B(12) levels were significantly higher in the oral (643 +/- 328 pg/ml; n = 18) compared with the intramuscular group (306 +/- 118 pg/ml; n = 15) at 2 months ($P < 0.001$) and 4 months (1005 +/- 595 versus 325 +/- 165 pg/ml; $P < 0.0005$) and both groups had neurological responses. In the other study, serum vitamin B(12) levels increased significantly in those receiving oral vitamin B(12) and intramuscular vitamin B(12) ($P < 0.001$).

The Conclusions: The evidence derived from these limited studies suggests that 2000 microg doses of oral vitamin B(12) daily and 1000 microg doses initially daily and thereafter weekly and then monthly may be as effective as intramuscular administration in obtaining short-term haematological and neurological responses in vitamin B(12)-deficient patients.

2) **Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency**: Wang H, Li L, Qin LL, Song Y, Vidal-Alaball J, Liu TH (2018).

There are three randomised controlled studies (clinical studies where people are randomly put into one of two or more treatment groups). The studies randomised 153 participants (74 participants to oral vitamin B_{12} and 79 participants to intramuscular vitamin B_{12}). Treatment duration and follow-up ranged between three and four months. The mean age of participants ranged from 39 to 72 years.

Two studies used 1000 µg/day oral vitamin B_{12} and showed no relevant difference to intramuscularly applied vitamin B_{12} with regard to vitamin B_{12} blood levels. One trial used 2000 µg/day vitamin B_{12} and showed higher vitamin B_{12} blood levels in favour of oral vitamin B_{12}. Two studies reported side effects. One study stated that no treatment-related side effects were seen in both the oral and intramuscular vitamin B_{12} groups. One study reported that 2 of 30 participants in the oral vitamin B_{12} group left the trial early due to side effects. Orally taken vitamin B_{12} showed lower treatment-associated costs than intramuscular vitamin B_{12} in one trial. No study reported on clinical signs and symptoms of vitamin B_{12} deficiency (e.g. fatigue, depression, neurological complications), health-related quality of life, or acceptability of the treatment scheme.

The overall quality of the evidence was low or very low, mainly due to the small number of included studies and the low numbers of participants in these studies.

The Authors' conclusions: Low quality evidence shows oral and IM vitamin B_{12} having similar effects in terms of normalising serum vitamin B_{12} levels, but oral treatment costs less. We found very low-quality evidence that oral vitamin B_{12} appears as safe as IM vitamin B_{12}. Further trials should conduct better randomisation and blinding procedures, recruit more participants, and provide adequate reporting. Future trials should also measure important outcomes such as the clinical signs and symptoms of vitamin B_{12} deficiency, health related quality of life, socioeconomic effects, and report adverse events adequately, preferably in a primary care setting.

3) **Effective treatment of cobalamin deficiency with oral cobalamin**: Kuzminski AM, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J (1998).

They investigated the efficacy of oral therapy. They randomly assigned 38 newly diagnosed cobalamin deficient patients to receive cyanocobalamin as either 1 mg intramuscularly on days 1, 3, 7, 10, 14, 21, 30, 60, and 90 or 2 mg orally on a daily basis for 120 days. Therapeutic effectiveness was evaluated by measuring hematologic and neurologic improvement and changes in serum levels of cobalamin (normal, 200 to 900 pg/mL) methylmalonic acid (normal, 73 to 271 nmol/L), and homocysteine (normal, 5.1 to 13.9 micromol/L). Five patients were subsequently found to have folate deficiency, which left 18 evaluable patients in the oral group and 15 in the parenteral group. Correction of hematologic and neurologic abnormalities was prompt and indistinguishable between the 2 groups. The mean pretreatment values for serum cobalamin, methylmalonic acid, and homocysteine were, respectively, 93 pg/mL, 3,850 nmol/L, and 37. 2 micromol/L in the oral group and 95 pg/mL, 3,630 nmol/L, and 40.0 micromol/L in the parenteral therapy group. After 4 months of therapy, the respective mean values were 1,005 pg/mL, 169 nmol/L, and 10.6 micromol/L in the oral group and 325 pg/mL, 265 nmol/L, and 12.2 micromol/L in the parenteral group. The higher serum cobalamin and lower serum methylmalonic acid levels at 4 months posttreatment in the oral group versus the parenteral group were significant, with $P < .0005$ and $P < .05$, respectively. In cobalamin deficiency, 2 mg of cyanocobalamin administered orally on a daily basis was as effective as 1 mg administered intramuscularly on a monthly basis and may be superior.

Conclusion:

After reviewing different studies, we came to the conclusion that:

High oral dose of Vitamin B12 is as effective as intramuscular injection of Vitamin B12 in achieving neurological and hematological response in vitamin B12 deficiency, and it can be superior in achieving better clinical results, with its convenience and cost-effective.

In our practice we switched many patients to oral vitamin B12, and patients achieved same hematological and neurological results, with low cost, and more convenient for them.

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