Oral Versus Intramuscular Cobalamin Treatment in Megaloblastic Anemia: A Single-Center, Prospective, Randomized, Open-Label Study

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ABSTRACT

Background: Cobalamin (vitamin B_{12}) deficiency, the most common cause of megaloblastic anemia, is treated with intramuscular (IM) cobalamin. It has been suggested by some investigators that oral (PO) cobalamin treatment may be as effective in the treatment of this condition, with the advantages of ease of administration and lower cost.

Objective: This study assessed the effects and cost of PO versus IM cobalamin treatment in patients with megaloblastic anemia due to cobalamin deficiency.

Methods: This was a 90-day, prospective, randomized, open-label study conducted at the Division of Hematology, Department of Internal Medicine, Adnan Menderes University Research and Practice Hospital (Aydin, Turkey). Patients aged ≥16 years with megaloblastic anemia due to cobalamin deficiency were randomized to receive 1000-μg cobalamin PO once daily for 10 days (PO group) or 1000-μg cobalamin IM once daily for 10 days (IM group). After 10 days, both treatments were administered once a week for 4 weeks, and after that, once a month for life. Patients were assessed for the presence of reticulocytosis between treatment days 5 and 10 until it was detected. Therapeutic effectiveness was assessed by measuring hematologic parameters on days 0, 10, 30, and 90 and serum vitamin B_{12} concentration on days 0 and 90. The Mini–Mental State Examination was used before and after the B_{12} therapy for cognitive function assessment and 125-Hz diapozone was used for vibration threshold testing. Neurologic sensory assessment, including soft-touch and pinprick examinations, was used to identify neuropathy at baseline and study end. Tolerability was assessed using laboratory tests and patient interview. Cost was assessed using the cost of the study drug and of the injection.

Results: Sixty patients completed the study: 26 in the PO group (16 men, 10 women; mean [SD] age, 60 [15] years) and 34 in the IM group (17 men, 17 women; mean [SD] age, 64 [10] years). Reticulocytosis was observed in all patients. In the PO group, at days 30 and 90, all hematologic parameters changed significantly versus day 0 (mean hemoglobin levels increased [both $P < 0.001$]; mean corpuscular volume decreased [both $P < 0.001$]; mean white blood cell count increased [day 30, $P < 0.01$; day 90, $P < 0.001$]; and mean platelet count increased [both $P < 0.001$]). The mean serum vitamin B_{12} concentration increased significantly from day 0 to 90 ($P < 0.001$). These hematologic parameters and the recovery patterns were similar between the 2 groups. Neurologic findings included sensitive peripheral neuropathy in 9 patients (15.0%), alteration of cognitive function (loss of memory, impaired concentration) in 7 patients (11.7%), and loss of sense of vibration in 5 patients (8.3%). Neurologic improvement was detected in 7 of 9 patients (77.8%) in the PO group and 9 of 12 patients (75.0%) in the IM group at day 30.

Conclusions: In this study of patients with megaloblastic anemia due to cobalamin deficiency, PO cobalamin treatment was as effective as IM cobalamin treatment. PO treatment also was better tolerated and less expensive compared with IM treatment. However, because of the small sample size and the short term of this study, further long-term studies are needed to determine the efficacy of PO cobalamin treatment. (*Clin Ther.* 2003;25:3124–3134) Copyright © 2003 Excerpta Medica, Inc.

Key words: vitamin B_{12} deficiency, megaloblastic anemia, oral cobalamin treatment.

INTRODUCTION

Cobalamin (vitamin B_{12}) deficiency is the most common cause of megaloblastic anemia.[1] Among patients aged >65 years, between 10% and 15% have cobalamin deficiency.[2,3] The daily requirement for cobalamin is ~2.4 µg.[4] The acidic environment of the stomach facilitates the breakdown of vitamin B_{12}. Intrinsic factor, which is released by parietal cells in the stomach, binds to vitamin B_{12} in the duodenum. This vitamin B_{12}–intrinsic factor complex subsequently plays a role in the absorption of vitamin B_{12} in the terminal ileum. This mechanism is responsible for ~60% of the absorption of cobalamin. In addition, an alternate system exists that is independent of intrinsic factor or even an intact terminal ileum: Cobalamin is absorbed by simple diffusion or mass action independent of intrinsic factor if 300- to 1000-µg/d cobalamin is administered orally (PO) or intramuscularly (IM) to patients with pernicious anemia. Approximately 1% of a large (300–100,000 µg/d) PO dosage of vitamin B_{12} is absorbed by this mechanism.[5,6]

The causes of cobalamin deficiency are pernicious anemia, food–cobalamin malabsorption, other malabsorption syndromes, nutritional deficiency, and other

gastrointestinal (GI) causes (eg, Zollinger-Ellison syndrome, Crohn's disease).[7] It typically presents as megaloblastic anemia. However, clinical manifestations may be related to hematologic, neurologic, and psychiatric symptoms and findings. Pancytopenia, peripheral neuropathy, gait disturbance, memory loss, irritability, depression, and psychosis are seen in these patients. In addition, these patients are at increased risk for myocardial infarction and stroke.[8,9] The standard treatment of cobalamin deficiency is monthly IM injections of at least 100 μg of B_{12}.[4] However, PO cobalamin treatment (>1000 μg/d) is also effective for pernicious anemia and other cobalamin-deficiency states due to simple diffusion or mass action,[10–14] with the advantages of ease of administration and lower cost.

The goal of this single-center study was to conduct an open-label, prospective, randomized trial to assess PO versus IM cobalamin therapy in patients with megaloblastic anemia due to cobalamin deficiency.

PATIENTS AND METHODS
Study Design

This was a 90-day, prospective, randomized, open-label study conducted at the Division of Hematology, Department of Internal Medicine, Adnan Menderes University Research and Practice Hospital (Aydin, Turkey). The local ethics committee approved the study protocol.

Patients

Patients aged ≥16 years with megaloblastic anemia due to cobalamin deficiency were enrolled between January 1999 and January 2003. Inclusion criteria were serum cobalamin concentration <160 pg/mL, megaloblastic anemia, and mean corpuscular volume (MCV) >94 fL (normal value, 80–94 fL). Exclusion criteria were vomiting and/or diarrhea, alcohol use >40 g/d, incapacity to provide informed consent, history of malignancy, folate deficiency, inability to ingest oral medication, and use of medication that might interfere with folate metabolism (eg, colchicines, methotrexate). Pregnant, possibly pregnant, or breastfeeding women were excluded from the study. All women of childbearing age were required to use an effective method of birth control throughout the study. All patients provided written informed consent to participate.

Methods
Treatment Regimens

Patients were assigned, using the block randomization method,[15] to 1 of 2 treatment groups. In the PO group, cobalamin* (1000-μg ampule mixed with 20 mL of fruit juice) was self-administered PO once daily for 10 days. We did not

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*Trademark: Cyanocobalamin® (Dodex, Deva, Turkey).

use cobalamin tablets because they were not available in Turkey at the time of this study. In the parenteral group, cobalamin (1000-μg ampule IM injection into the gluteus muscle) was administered once daily for 10 days (IM group). After 10 days, both treatments were administered once a week for 4 weeks, and then once a month for life. An experienced nurse administered the injections.

All patients were interviewed and examined by the same physician at study days 0, 10, and 30 of treatment. Complete blood cell count was performed by a hematologist using the Coulter Counter (Beckman Coulter, Inc., Fullerton, California) automatic blood analyzer system[16] at days 0, 10, and 30. Serum cobalamin concentrations were determined using chemiluminescence assay[17] at days 0 and 90. Serum autoantibodies to gastric parietal cells were investigated using indirect immunofluorescence via enzyme-linked immunosorbent assay (ELECYS kit, Hoffmann-La Roche Inc., Basel, Switzerland) at the beginning of the study.[18] In some patients, upper GI endoscopic examination and biopsy were performed before treatment by a gastroenterologist who was blinded to treatment assignment. GI endoscopy was performed in patients who could tolerate it, using the EG-2940 video endoscopy system (Pentax USA, Inc., Englewood, Colorado). A rapid urease test (model 2171, Quélab Laboratories, Inc., Montreal, Québec, Canada) was performed on gastric biopsy specimens, and a light microscope (Olympus BH2, Olympus Japan Co., Ltd., Tokyo, Japan) was used to perform the histopathologic examinations. Gastric atrophy was identified according to the Kekki classification.[19] Reticulocyte counts were calculated between days 5 and 10 until reticulocytosis was detected. The Mini–Mental State Examination[20] was given before and after B_{12} therapy for cognitive function assessment, and 125-Hz diapozone was used for vibration threshold testing at days 0 and 90. Neurologic sensory assessment, including soft-touch and pinprick examinations, was used to identify neuropathy at baseline and study end.

Response Criteria

Detection of reticulocytosis between days 5 and 10, and recovery of the hematologic parameters on complete blood counts and peripheral blood smears at days 10, 30, and 90 of treatment, were used to monitor the response to therapy. The primary end points were hemoglobin (Hb) level and improvements in signs and symptoms of anemia.

Tolerability

Tolerability was assessed by a hematologist at days 0, 30, and 90 using laboratory tests (eg, serum potassium level, eosinophilia on blood smear) and patient interviews.

Cost

Cost was assessed by the authors using the cost of the study drug and of the injections.

Statistical Analysis

Wilcoxon and Mann-Whitney U tests were used to compare the oral and parenteral treatment arms. Pretreatment and posttreatment values were compared using the 2-paired t test. Nominal variables were compared using the Yates chi-square test. P values < 0.05 were considered statistically significant. The Statistical Package for Social Sciences version 10.0 (SPSS Inc., Chicago, Illinois) was used to calculate the data.

RESULTS

Of 70 patients enrolled in the study, 10 were excluded because of failure to appear for follow-up after 10 days of treatment. The PO group comprised 26 patients (16 men, 10 women; mean [SD] age, 60 [15] years [range, 32–84 years]). The IM group comprised 34 patients (17 men, 17 women; mean [SD] age, 64 [10] years [range, 36–87 years]). The age, sex, pretreatment Hb level, platelet and white blood cell (WBC) counts, MCV, and serum cobalamin and folate levels were not significantly different between the 2 groups (Table). Reticulocytosis was observed in all patients.

Baseline Characteristics

Hematologic Findings

At baseline, all patients had abnormally low Hb and cobalamin concentrations (<12.0 g/dL and <160 pg/mL, respectively). The mean (SD) Hb concentration, MCV, WBC count, platelet count, and vitamin B_{12} concentration were 8.4 (2.1) g/dL, 112.3 (11.4) fL, 5.4 (2.0) cells × 10^3/µL, 172 (89) cells × 10^3/µL, and 72.9 (54.8) pg/mL, respectively, in the PO group, and 8.3 (2.3) g/dL, 114.8 (10.9) fL, 5.4 (2.7) cells × 10^3/µL, 159 (104) cells × 10^3/µL, and 70.2 (59.1) pg/mL, respectively, in the IM group. Serum folate levels were normal (5–25 ng/mL) in all patients.

Neurologic Findings

At the beginning and end of treatment, neurologic clinical findings included sensitive peripheral neuropathy (n = 9 [15.0%]), altered cognitive function (loss of memory, impaired concentration) (n = 7 [11.7%]), and loss of vibration sense (n = 5 [8.3%]). Because of cost, antiparietal cell antibodies were investigated in only 19 patients (14 and 5 in the PO and IM groups, respectively). Results were positive in 11 patients (57.9%) (8 and 3 patients in the PO and IM groups, respectively). Schilling's test and intrinsic factor level measurement were not investigated because these assessments could not be performed at the study site.

Endoscopic and Histologic Findings

In the PO cobalamin group, upper GI endoscopy was performed in the 18 patients (69.2%) who could tolerate it. Atrophic gastritis was observed in 5 patients (27.8%); other endoscopic findings included chronic antral gastritis (5 patients

3128

Table. Baseline demographic characteristics and hematologic response to treatment in study patients (N = 60).[*]

Parameter	PO Group (n = 26)	IM Group (n = 34)
Age		
Mean (SD)	60 (15)	64 (10)
Range	32–84	36–87
Sex, no. (%)		
Men	16 (61.5)	17 (50.0)
Women	10 (38.5)	17 (50.0)
Serum vitamin B_{12} concentration, mean (SD), pg/mL (NV, 160–950)		
Day 0	72.9 (54.8)	70.2 (59.1)
Day 90	213.8 (30.2)[†]	225.5 (40.2)[†]
Hb level, mean (SD), g/dL (NV, 14.0–17.5)		
Day 0	8.4 (2.1)	8.3 (2.3)
Day 10	9.8 (2.0)[†]	9.7 (2.2)[†]
Day 30	12.2 (1.2)[†]	12.2 (1.3)[†]
Day 90	13.8 (0.7)[†]	13.7 (0.9)[†]
MCV, fL (NV, 80–94)		
Day 0	112.3 (11.4)	114.8 (10.9)
Day 10	105.6 (13.1)[‡]	106.9 (12.1)[†]
Day 30	90.0 (10.0)[†]	89.6 (8.7)[†]
Day 90	86.9 (3.9)[†]	86.7 (4.1)[†]
WBC count, cells $\times$ 10^3/μL (NV, 1.8–7.8)		
Day 0	5.4 (2.0)	5.4 (2.7)
Day 10	4.4 (2.0)[‡]	6.6 (2.5)[§]
Day 30	7.1 (2.3)[‖]	7.0 (2.2)[†]
Day 90	7.9 (1.2)[†]	7.7 (1.5)[†]
Platelet count, cells $\times$ 10^3/μL (NV, 150–450)		
Day 0	172 (89)	159 (104)
Day 10	236 (114)[‡]	223 (144)[†]
Day 30	277 (111)[†]	239 (98)[†]
Day 90	311 (94)[†]	274 (78)[†]

PO = oral; IM = intramuscular; NV = normal value; Hb = hemoglobin; MCV = mean corpuscular volume; WBC = white blood cell.

[*]No significant between-group differences were found.

[†]$P < 0.001$ versus day 0.

[‡]$P < 0.005$ versus day 0.

[§]$P < 0.05$ versus day 0.

[‖]$P < 0.01$ versus day 0.

[27.8%]), chronic pangastritis (3 patients [16.7%]), enterogastric reflux (2 patients [11.1%]), and alkaline reflux gastritis (2 patients [11.1%]); 1 patient (5.6%) had no abnormalities on endoscopy (some patients had >1 of these findings). Upper GI endoscopy was performed in 27 patients (79.4%) in the IM group; findings included atrophic gastritis (9 patients [33.3%]), chronic pangastritis (4 patients [14.8%]), alkaline reflux gastritis (4 patients [14.8%]), chronic antral gastritis (2 patients [7.4%]), enterogastric reflux (2 patients [7.4%]), and erosive gastritis (1 patient [3.7%]); 5 patients (18.5%) had no abnormalities. Rapid urease testing detected *Helicobacter pylori* infection in 7 of 18 patients (38.9%) in the PO group and 7 of 27 patients (25.9%) in the IM group. Fifteen patients (25.0%) refused to undergo upper GI endoscopy (8 [30.8%] and 7 [20.6%] patients in the PO and IM groups, respectively).

Histopathologic examination in 17 of 26 patients (65.4%) who received PO cobalamin revealed atrophic gastritis in 6 patients (35.3%), antral gastritis plus intestinal metaplasia in 4 patients (23.5%), atrophic gastritis plus intestinal metaplasia in 3 patients (17.6%), antral gastritis in 2 patients (11.8%), and superficial gastritis in 2 patients (11.8%). Histopathologic examination was performed in the 27 of 34 patients (79.4%) who underwent GI endoscopy in the IM group; atrophic gastritis was established in 9 patients (33.3%), atrophic gastritis plus intestinal metaplasia in 9 patients (33.3%), superficial gastritis in 4 patients (14.8%), antral gastritis plus intestinal metaplasia in 3 patients (11.1%), and antral gastritis in 1 patient (3.7%). One patient in the IM group had no abnormalities on histologic examination. Gastritis and/or metaplasia was detected in the biopsy samples of 26 of 44 patients (59.1%) who underwent pathologic examination. Histologic examination of gastric biopsy samples detected *H pylori* infection in 7 of 17 patients (41.2%) in the PO group and in 9 of 27 patients (33.3%) in the IM group.

Etiology of Cobalamin Deficiency

Poor dietary animal protein intake was found as the cause of vitamin B_{12} deficiency in 4 (15.4%) and 5 (14.7%) patients in the PO and IM cobalamin groups, respectively. A vegetarian diet was found to be the cause in 2 patients (1 each in the PO and IM groups); 7 patients (3 and 4 patients in the PO and IM groups, respectively) experienced poor nutrition due to a lack of money to buy food. None of the patients had a history of or current gastric or ileal surgery, diarrhea, pancreatic insufficiency, or drug use. Although we did not assess intrinsic factor for pernicious anemia, we investigated antiparietal cell antibody only in 14 patients (41.2%) in the PO group, 8 of whom (57.1%) had positive results, and in 5 patients (19.2%) in the IM group, 3 (60.0%) of whom had positive results. This analysis could not be performed in all patients due to cost. In patients with positive results, we thought that the cause of cobalamin deficiency may have been food–cobalamin malabsorption or pernicious anemia due to advanced age and histologic findings, and we excluded all other possible causes.[21–23]

Hematologic and Neurologic Responses

The Hb level, WBC count, and platelet count were increased significantly at days 30 and 90 (all $P < 0.001$ except WBC count at day 30 in the PO group; $P < 0.01$).

Cognitive function dramatically improved in 3 patients (11.5%) in the PO group and 4 patients (11.8%) in the IM group after day 10. Improvement of sensitive neuropathy in 2 of 4 patients (50.0%) was documented in the PO treatment group and in 3 of 5 patients (60.0%) in the IM group at day 30. Improvement of vibration sense occurred in both patients (100.0%) in the PO group and in 2 of the 3 patients (66.7%) in the IM group. No statistically significant differences were found between the 2 groups in improvement of cognitive function, sensitive neuropathy, or vibration sense.

Tolerability

No treatment-related adverse events were reported in either treatment group.

Cost

The costs per treatment (study drug + injection in the IM group) were $80 US and $220 US per person in the PO and IM groups, respectively ($P < 0.001$).

DISCUSSION

In most countries, the current treatment of vitamin B_{12} deficiency is IM injection. However, parenteral cobalamin treatment is painful, and the injections pose a risk for needle-stick injuries. In addition, administration of IM injections often adds to the cost of therapy.[5] Therefore, PO treatment of cobalamin deficiency may be preferred for these patients or for those with megaloblastic anemia related to cobalamin deficiency.[5] PO cobalamin treatment was first administered for cobalamin deficiency in 1968 by Berlin et al[10] in Sweden, and although it is still widely used there, it is not in the United States. The percentage of internists in Sweden who ever used PO cobalamin to treat megaloblastic anemia increased from 0% in 1989 to 19% in 1996. The percentage of internists who were aware of an effective PO cobalamin preparation for the treatment of cobalamin deficiency also increased significantly, from 4% to 29% ($P < 0.001$).[24,25]

The results of the current study showed that both PO and IM cobalamin treatments were equally effective in megaloblastic anemia.

Several studies[11,26–29] of PO treatment of cobalamin deficiency have been conducted. One small, prospective, randomized study[11] compared PO with IM cobalamin therapy in 38 patients with cobalamin deficiency due to various causes. In that study, patients in the IM therapy group received vitamin B_{12} 1000 µg IM on study days 1, 3, 7, 10, 14, 21, 30, 60, and 90, and those in the PO treatment group received 2000 µg once daily for 4 months. The results showed that PO cobalamin was as effective as conventional injection therapy.

Some investigators conducted prospective, open-label studies to assess the response to PO cobalamin therapy with food–cobalamin malabsorption. Verhaeverbeke et al[26] administered PO cobalamin to 94 patients, and serum cobalamin concentration normalized after 30 days in 88% of patients. Andres et al[27] prospectively studied 10 patients with cobalamin deficiency, and they had established improvement in the patients treated with 3000 or 5000 μg of PO cobalamin once a week for at least 3 months. After 3 months of treatment, all patients had increased Hb levels. Recently, Andres et al[28] also reported the preliminary results of 30 patients with cobalamin deficiency. In that study, patients were treated with 250 to 1000 μg/d of PO crystalline cobalamin for >1 month. During the first month of treatment, 54% of the patients achieved normal Hb levels and decreased MCV.

The efficacy of oral vitamin B_{12} treatment also was demonstrated in children with selective vitamin B_{12} malabsorption (Imerslund-Graesbeck syndrome).[29] In addition to PO and IM cobalamin supplementation, sublingual therapy is another treatment modality for cobalamin deficiency. In one such study,[30] sublingual cobalamin (2000 μg/d for 7–12 days) was given to 18 patients with cobalamin deficiency but without anemia. Normalization of serum cobalamin concentration was detected in all patients. This modality is applicable in patients with cobalamin deficiency who refuse parenteral cobalamin treatment, in patients with diarrhea and/or vomiting, and/or in patients who are unable to take oral medication.

Most of these studies[23,25,28–30] did not include a control group, however, so the results should be interpreted with caution. In addition, our study used a small sample size and was short term; future studies with larger sample sizes and a longer study period should be conducted to examine the usefulness of oral cobalamin.

CONCLUSION
In this study of patients with megaloblastic anemia due to vitamin B_{12} deficiency, a moderate dose PO cobalamin treatment was as effective as IM cobalamin treatment. PO treatment was also better tolerated and less expensive compared with IM treatment.

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