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EFFICACY OF ORAL AND INTRAMUSCULAR VITAMIB B12 IN EARLY RESPONSE AND PREFERENCES OF PATIENTS

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ABSTRACT

BACKGROUND: Deficiency of vitamin B_{12} can be managed by oral substitution or intramuscular injection of vitamin B_{12}. When different administration routes are present, the preference of patients should also be considered while treatment selection.

OBJECTIVE: The main objective of our study was to assess the preferences of patients towards intramuscular injection or oral treatment of vitamin B_{12} supplementation, and to confirm the efficacy of both treatment options in patients.

METHODOLOGY: This was a prospective clinical trial, conducted at tertiary care hospital for a period of one year (June 2020 to May 2021). A total of 42 patients were selected for study. Patients were randomly and equally allocated to oral (21 patients) or intramuscular treatment groups (21 patients). In Group A, patients were given oral tablets of 1000µg cyanocobalamin, while in Group B, 1000µg hydroxocobalamin injections were given to patients. Samples of whole blood were extracted before starting of treatment, followed by 1, 2 and 4 weeks of treatment, and were analyzed for serum vitamin B_{12} levels. Before and after treatment, the patients were asked to fill questionnaire regarding preference of treatment options. SPSS 24.0. was used for analysis. A p-value of <0.05 was considered as statistically significant.

RESULTS: Among all patients, the mean age was found as 46.3±3 years with majority were including the females (63.3%). In Group A, serum vitamin B_{12} levels were 155 pmol/L (range 144-181) and Group B, it was 161 pmol/L (range 149-169). After 1 month of therapy, the level

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of serum vitamin B_{12} level was increased significantly in Group A (368; range 295-419) and Group B (2881 (range 1297-4418). Before starting of treatment, most of the preference was given to oral route of administration. Eight patients changed their opinion after therapy.

CONCLUSION: There was significant difference in levels of vitamin B_{12} in both oral and intramuscular treatment groups. Due to obvious effect in response to treatment, the opinion of patients to select the routes of administration was also changed.

Keywords: Vitamin B_{12}, Oral therapy, Intramuscular therapy, Preference, Cyanocobalamin.

INTRODUCTION

Vitamin B_{12} deficiency is common clinical entity, widely presents in combination with other conditions or isolated. The overall prevalence in adults is 8-16%, while in elderly, it is 5-40%. [1-2] Though the actual prevalence in global population is still not known, although it seems to increase with age, mostly due absorption impairment. [3-4]

Various causes may lead to deficiency of vitamin B_{12} including nutritional/dietary, malabsorption, and other causes related to gastrointestinal tract. [5-6] Pernicious anemia is usually presented as hematological clinical features and is related to intrinsic factors antibodies and/or gastric parietal cells antibodies, though it contributes a minor amount of cause of vitamin B_{12} deficiency. [7] Additionally, defect in mechanisms of transport because of genetic factors are also among minor causes. [8] Therapy with metformin and acid-lowering agents may take part in etiology of vitamin B_{12} deficiency.

There are various clinical presentations associated with deficiency of vitamin B_{12}. In addition to non-specific symptoms including loss of appetite and tiredness, neurological diseases (i.e., ataxia, polyneuropathy), hematological diseases (i.e., megaloblastic anemia), and psychiatric problems (i.e., depression) may also be seen. [8, 12] Cardiovascular problems in association with hyperhomocysteinemia may also present. [13-16] As deficiency of vitamin B_{12} is not an irreversible cause of demyelinating diseases and failure of bone marrow, early detection and adequate treatment are essential. [12]

Various causes make indications for treatment by vitamin B_{12} supplementation, including dietary deficiency, pernicious anemia, and gastrectomy). [12] In pregnancy females on Mediterranean diet, patients with nitrous oxide exposure and gastric surgery, and patients on pure vegetarian diet may be treated prophylactically. [17] Although, official threshold for starting of treatment is not established yet. On laboratory methods, the deficiency of vitamin B_{12} is defined as borderline to subnormal level of vitamin B_{12} in serum. Holotranscobalamin is a bioactive state of vitamin B_{12} is considered as more sensitive and specific marker of vitamin B_{12} deficiency. [18-20] Functional deficiency of vitamin B_{12} is recognized by high homocysteine and/or methylmalonic acid. Functional analysis is considered when there is high suspicion of

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vitamin B_{12} deficiency, moderately low levels of vitamin B_{12}, in patients having unexplained neurological problems or macrocytosis, or when deficiency of vitamin B_{12} is highly possible as manageable cause of dementia in patients. [17] Subclinical deficiency of vitamin B_{12} is present in 10-25% of aged population. [17]

The management of vitamin B_{12} deficiency include vitamin B_{12} supplementation by either oral or intramuscular route of administration. In patients with severe deficiency of vitamin B_{12}, 1000µg injection should be given several times in a week for 1-2 weeks, followed by weekly and monthly injections. [12, 17] In patients with dietary deficiency of mild malabsorption, initial high dose oral treatment can be given. [12] As the absorption of vitamin B_{12} is not predictable in severe cases or when frequent monitoring is required, initial parenteral route should be used, followed by oral route after normalization of serum vitamin B_{12} levels. [17]

In western countries, supplementation of vitamin B_{12} is mainly given as intramuscular injections. [21] Though, evidence of good effectiveness of oral supplementation is available, there is no high-dose oral vitamin B_{12} monopreparation available. [22-24] Even in the presence of gastrointestinal diseases, oral vitamin B_{12} treatment shows satisfactory response. A study revealed that deficiency of vitamin B_{12} can be inverted in patients undergone gastrectomy. [25] Although there is limited data available for effectiveness of high oral dose of vitamin B_{12} supplementation in comparison to intramuscular route. [26]

As compared to intramuscular route, oral vitamin B_{12} may show cost-effectiveness and patient acceptance. [27] Preferences of patients in treatment decision should also be considered. [28] Additionally, a better sense of patient values and preferences to make choice is basic for achievement of shared making of decision and eventually enhancing the adherence.

This study aimed to evaluate preference of vitamin B_{12} treatment by intramuscular or oral route, and to validate the effectiveness of early biomarker for monitoring of oral treatment with vitamin B_{12} supplementation.

PATIENTS AND METHODS

This was a randomized controlled trial, conducted at tertiary care hospital. The study was conducted for a period of one year (June 2020 to May 2021).

Participants

Patients were randomly and equally allocated to oral (21 patients) or intramuscular treatment groups (21 patients). Patients with serum vitamin B_{12} concentration of <200 pmol/L, age ≥18 years and who gave consent were included in this study. Patients taking vitamin supplementation including vitamin B_{12}, or who has history of dementia, known defects of hereditary transcobalamin transportation were excluded from the study.

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Interventions

In patients with oral treatment group, one tablet (1000µg) cyanocobalamin was instructed daily for 28 consecutive days. In patients with intramuscular treatment group, conventional treatment with injection of 1000µg hydroxocobalamin weekly was instructed.

Outcomes of Adherence

The adherence rates were calculated as (i) adherence with count of pills, which is explained as percentage of days with performed pill intakes divided by days of prescribed pill intakes, and (ii) irregularities of dosing, which is explained as percentage of days with ≥2 events of dosing.

Assessment of Biomarkers

Venous whole blood samples were extracted prior to initial administration (V0), followed by after 1 (V7), 2 (V14), and four weeks of treatment (V28). The blood samples were transported in two collection tubes. For hematological analysis, blood samples were collected in EDTA-containing tube and were analyzed using automated hematology analyzer. The other samples were collected in clot activator tubes for analysis of folate and vitamin B_{12} levels using automated immunoassay analyzer.

Preferences of Patients

The preferences of patients were determined before randomization (V0) and after four weeks of treatment (V28). Patients were asked to choose oral, injectable or no preference by the help of questionnaire. The questionnaire contained various items including disgust, pain, effectiveness, side effects, difficulties, inconveniences, costs, time consumption, and nonadherence to scheduled treatment.

Statistical Analysis

Quantitative values are shown as mean, standard deviation, median and percentages. To compare the numerical variables between two groups, Mann-Whitney test was used and for three groups, Kruskal-Wallis test was used. A p-value of <0.05 was considered as statistically significant.

RESULTS

A total of 42 patients were selected for the study and were divided into oral group (n=21), and intramuscular group (n=21). The baseline characteristics of both groups are summarized table 1. Comparison of vitamin B_{12} levels was done between both groups. At day 0 visit, initial baseline value was approximately equal with no significant changes. Though the levels were remarkably high in intramuscular group at consecutive day 7, 14, and 28 ($p<0.001$)

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(Table 2). Preference of patients was also analyzed. Majority of patients preferred oral route of administration over intramuscular due to various factors (Table 3). Majority of patients were having concern regarding pain, disgust, side effects, inconvenience, and time consumption. Few patients changed their preference after therapy.

Table 1: Baseline Characteristics of Patients (n=42)

Parameter	**Group O-Oral (n=21)**	**Group I-IM (n=21)**	**p-value**
Age (years)	45.23 ± 12.44	47.32 ±13.12	0.32
Body mass index (kg/m^2)	28.18 ± 6.56	27.97 ± 7.43	0.41
Vitamin B_{12} levels (pmol/L)	141 ± 23.41	144 ± 20.39	0.48

Table 2: Comparison of Levels of Vitamin B12 (pmol/L) at Consecutive Visit Days (n=42)

Visit Day	**Group O-Oral (n=21)** *(pmol/L)*	**Group I-IM (n=21)** *(pmol/L)*	**p-value**
Day 0	155	161	0.48
Day 7	310	1103	<0.001
Day 14	331	1788	<0.001
Day 28	368	2881	<0.001

Table 3: Preference of Patients and Associated Factors in Choosing Treatment (n=42)

Parameter		**Prefers Oral (n=24)**	**Prefers IM (n=8)**	**No preference (n=12)**	**p-value**
Pain	Syringes	5.1 ± 1.88	3.3 ± 1.4	2.4 ± 1.1	0.001
	Tablets	1.1 ± 0.01	2.0 ± 2.1	1.0 ± 0.2	0.112
Repulsion	Syringes	5.8 ± 2.2	3.2 ± 2.1	3.1 ± 2.1	0.005
	Tablets	3.2 ± 1.6	4.7 ± 2.3	2.4 ± 1.2	0.034
Side effects	Syringes	4.4 ± 2.1	2.3 ± 1.5	2.4 ± 1.4	0.011
	Tablets	2.1 ± 1.1	2.6 ± 2.1	2.3 ± 1.2	0.054
Effectiveness of Treatment	Syringes	8.1 ± 1.3	8.9 ± 1.0	8.6 ± 1.4	0.65
	Tablets	7.3 ± 2.4	6.7 ± 2.1	7.8 ± 1.4	0.44
Inconvenience	Syringes	6.6 ± 1.6	2.5 ± 1.3	2.5 ± 1.1	<0.001
	Tablets	2.6 ± 1.3	4.9 ± 2.2	2.3 ± 1.8	0.019
Difficulties	Syringes	4.8 ± 2.6	1.9 ± 1.6	1.5 ± 0.9	0.002

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	Tablets	1.8 ± 1.7	1.8 ± 1.3	1.2 ± 0.5	0.854
Consumption Time	Syringes	7.2 ± 2.4	4.3 ± 2.5	2.5 ± 1.1	<0.001
	Tablets	1.3 ± 0.3	2.5 ± 1.0	1.4 ± 1.0	0.002
Cost Effectiveness	Syringes	4.7 ± 2.3	4.1 ± 2.8	3.7 ± 2.6	0.601
	Tablets	2.9 ±1.6	2.6 ± 1.6	2.3 ± 2.5	0.552
Non-adherence to treatment	Syringes	3.5 ± 2.4	3.9 ± 2.6	2.9 ± 2.9	0.411
	Tablets	2.5 ± 2.5	4.6 ± 1.9	2.8 ± 2.3	0.02

DISCUSSION

In current study, the level of vitamin B_{12} was increased after 28 days of oral and/or intramuscular high – dose vitamin B_{12} therapy. Other studies also support these findings, in which two trials assessed effect of high – dose oral vitamin B_{12} therapy in comparison of placebo [24, 29-30], while three trails compared oral vs intramuscular vitamin B_{12} therapy. [22-23, 31]

In disparity of other studies, we detected increased response after intramuscular administration, hence the theory of non-inferiority of oral administration in comparison of intramuscular administration should not be accepted. The reason of high response may be due to use of hydroxocobalamin, which is intermediate form that is widely accessible to cells in contrast to other forms of cobalamin. [32] In pediatric patients with deficiency of vitamin B_{12}, one intramuscular injection of hydroxocobalamin (400µg) improved the motor function and repletion of cobalamin. [33] Furthermore, retention of hydroxocobalamin is longer in plasma in comparison to other cyanocobalamin doses, allowing the less frequency of dosing. Although, due to low stability of hydroxocobalamin, it is less suitable for oral administration, therefore, cyanocobalamin is used commonly for oral administration as it is inexpensive and more stable. [34] Sustainability of the biomarker response after intramuscular hydroxocobalamins has not understood completely. In a study, among 8 patients with vitamin B_{12} deficiency having levels <80pg/mL, vitamin B_{12} levels were increased to 300-1100 pg/mL after 10 days of high – dose intramuscular hydroxocobalamin. [35] In our study, wide variation response of vitamin B_{12} was seen within intramuscular group, which relates to various individual variations in pharmacokinetics of hydroxocobalamin mentioned by others. [36-37]

There are no studies available for increased levels of vitamin B_{12} with daily oral vitamin B_{12} administration over longer period of treatment same as that observed after intramuscular administration. In a study, high-dose oral vitamin B_{12} administration for 3 months increased the vitamin B_{12} levels in patients having initial low levels as compared to our study in which similar response was seen in 28 days. [30] Continuation of the therapy did not change the levels of vitamin B_{12} significantly up to 6 months. [30] One study demonstrated a highland in serum vitamin B_{12} levels (mean = 1164 pg/mL) after treatment of 3 months with high – dose hydroxocobalamin and consequent treatment up to 18 months with high – dose oral

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cyanocobalamin. [38] These findings explained that continuous treatment with high – dose oral vitamin B_{12} reaches serum vitamin B_{12} saturation after treatment of 3 months. In current study, four patients did not reach normal vitamin B_{12} levels after oral administration. Although, two of those patients had normal levels at day 14 visit, followed by decline afterwards. Keeping rational reasons aside e.g., compliance etc., these results suggest that saturation time of vitamin B_{12} may vary among patients. Remaining two patients responded slowly, suggestive of underlying cause of vitamin B_{12} deficiency. Additionally, active part of vitamin B_{12} reached the normal value at visit day 28. One of the reasons of non-responsiveness in oral group could be pernicious anemia. Although, as all patients showed some response or reached physiological rationale for slow response, this hypothesis was less likely to be true.

After treatment with intramuscular hydroxocobalamin, the supratherapeutic levels were observed, which may not be possible with oral administration. Furthermore, normalization of all parameters was seen more in intramuscular group as compared to oral group. Although, in oral group, incomplete response was limited to vitamin B_{12}. Therefore, the advantage of such increased response to intramuscular therapy seems limited to practice use in the state of decreased administrations e.g., long intervals in treatment, and when symptomatic patient requiring quick normalization of markers. Further studies should be performed for assessment of effects of various cobalamin forms on biomarkers and clinical outcomes. As so, obtained variations between different forms of cobalamin should be included in vitamin B_{12} treatment guidelines.

As traditionally expected, the preference of patients was oral administration, both before and after completion of treatment. Other studies were also in line with our findings in terms of oral treatment preferences. [38-39] In one study, 83% patients preferred oral administration in comparison to intramuscular. [38] In other study, the patients were being treated by intramuscular route, but they were willing to switch to oral treatment. Major factors to switch from intramuscular to oral route was high cost, disadvantage of injections, and convenience with oral therapy. [39] In our study, we observed inconvenience and time consumption of intramuscular treatment as compared to oral administration.

There was slight variation in patient preference after getting oral treatment, whereas variation occurred only in favor of oral administration. This suggests that patients value the administration route more after experiencing treatment with oral route in firsthand. After receiving intramuscular treatment, the change in preference was observed in few patients in different directions. In terms of increased intramuscular treatment response, the needed frequency of injections in clinical scenario may be decreased in mild deficiency of vitamin B_{12}. Further studies with validated methods are required to achieve insight preference of patients.

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CONCLUSION

Variations in level of vitamin B_{12} were increased than expected levels. Hence, theory of non-inferiority oral therapy should not be used. Effects of biomarker at midterm and preferences of patients should be considered while choosing the treatment plan of patients. Initial preferences of oral and/or intramuscular route may vary over time and explains frequent re-assessment of patient preferences. However, many patients preferred oral administration prior to and after therapy. Additional studies may help for evaluation regarding route of administration.

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