ORIGINAL ARTICLE

CHRONIC DIARRHOEA: NOT A RARE PRESENTATION OF VITAMIN B 12 DEFICIENCY

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Background: Diarrhoea is defined as stool frequency of more than three times in twenty-four hours or a stool weight of more than two hundred grams and it is labelled as chronic diarrhoea if it persists for more than four weeks. Chronic diarrhoea is a common gastrointestinal problem worldwide that affects three to fifteen percent of population. **Objective was** to determine the efficacy of vitamin B 12 replacement in treatment of chronic diarrhoea in vitamin B deficient patients. It was a Quasi-experimental study carried out at Pakistan Ordinance Factory (POF) Hospital Wah Cantt, from September 2023 to February 2024. **Methods:** All the new patients of chronic diarrhoea of ages between 12–65 years who had low serum vitamin B 12 and normal serum folate levels were included in the study. The patients were booked from Medicine and Allied outpatient and they were given parenteral vitamin B12. The sub-set of patients in whom diarrhoea was settled was followed up till six months. The efficacy was defined as settlement of diarrhoea with parenteral vitamin B12 within one week. The secondary outcomes were adequacy of serum vitamin B12 levels at 2 weeks, three months and six months after treatment. All patients (100%) had adequate B12 levels till follow up. Data was analyzed through SPSS. **Results:** Efficacy of parenteral B12 supplementation was seen in 16 (76.2%) patients. Out of sixteen patients who responded to vitamin B12 supplementation, 10 (47.6%) patients showed improvement in less than two days, 5 (23.8%) showed improvement in less than four days and 1 (4.8) patient stopped experiencing diarrhoea within seven days of intramuscular vitamin B12 with *p*-value of <0.001.

Conclusion: Replacement of vitamin B 12 in patients with chronic diarrhoea having low vitamin B 12 results in settlement of diarrhoea.

Keywords: Chronic diarrhoea; Vitamin B 12

Citation: Adil N, Mehraj A, Khan J, Bhutta S, Jamil M, Aslam M. Chronic Diarrhoea: Not a rare presentation of vitamin B 12 deficiency. J Ayub Med Coll Abbottabad 2024;36(1):155–9.

DOI: 10.55519/JAMC-01-13026

INTRODUCTION

Diarrhoea is defined as stool frequency of more than three times in twenty-four hours or a stool weight of more than two hundred grams and it is labelled as chronic diarrhoea if it persists for more than four weeks.[1] Chronic diarrhoea is a common gastrointestinal problem worldwide that affects three to fifteen percent of population.[2] Aetiology of chronic diarrhoea is diverse. A variety of disease conditions are associated with it such as drugs, gastrointestinal interventions, structural abnormalities of intestine, inflammatory or neoplastic pancreato-biliary diseases or functional intestinal disorders such as irritable bowel syndrome[3]. Vitamin B 12 deficiency is also one of the causes of chronic diarrhoea, but it is underrated and underreported and it is thought to be as rare presentation of vitamin B 12 deficiency. As there is a rapid turnover of the enterocytes in patients with diarrhoea so it is plausible that diarrhoea may be a manifestation of enteropathy due to vitamin B 12 deficiency.[4]

Vitamin deficiencies cause various impacts on human health but B 12 deficiency has multitude of multisystem manifestations including haematological, neurological and neuropsychiatric.[5] Cyanocobalamin or Vitamin B12 is one of the water-soluble vitamins that is mostly found in food obtained from animal resources and cannot be synthesized in the human body. It has a fundamental function in synthesis of human deoxyribonucleic acid (DNA). Working closely with folic acid, vitamin B 12 serves as a crucial co-factor in synthesis of DNA and RBCs. It enhances the neuronal function and its deficiency leads to poor neurological outcomes.[6] Deficiency of this vital nutrient is associated with haematological, cardiovascular, neurological, cutaneous, psychiatric and gastrointestinal complications. Its deficiency is found in population among all age groups.[7] In Pakistan, no data exists on prevalence of vitamin B 12 deficiency. However, it B12 deficiency was found to be almost seven percent in adult males and females of middle during study of a small cross-section of

Pakistani population.[8] Vitamin B 12 deficiency usually presents in its usual form but sometimes it is very difficult to suspect it due to atypical manifestations. One of the atypical presentations of vitamin B-12 deficiency is chronic diarrhoea, which is said to be a rare manifestation.[9] While haematological, neurological and psychiatric manifestations associated with vitamin B 12 deficiency are well documented, there is paucity of data on the existence of chronic diarrhoea associated with vitamin B 12 deficiency. It is commonly seen in patients presenting with chronic diarrhoea in Department of Medicine & Allied at POF hospital Wah Cantt. It is our observation that replenishment of only vitamin B 12 subsides chronic diarrhoea. Vitamin B 12 deficiency and chronic diarrhoea are frequently found hand in hand in clinical practice.[10] However, there has been no comprehensive work done regarding role of vitamin B12 in causation or treatment of chronic diarrhoea. As there is limited work done regarding association of vitamin B 12 deficiency and diarrhoea in local population, we started our study after the clinical observations made at POF hospital Wah and scant evidence available in case reports and some international studies. This study will be first local study measuring the efficacy of vitamin B12 in treatment of chronic diarrhoea. This study will guide us about management and prevention of chronic diarrhoea and will help to improve quality of life of patients.

MATERIAL AND METHODS

We took permission of hospitals ethical committee first which endorsed our research with ERC number: WMC/ERC/IRB/040. We performed our Quazi-experimental study at department of Medicine and Allied of POF hospital Wah Cantt, from September 2023 to February 2024. We calculated sample size with help of sample size calculator keeping significance level: 5%, Power of test: 90, the anticipated frequency of diarrhoea with adequate serum B12 levels to be 3%[11] and anticipated frequency of diarrhoea with inadequate B12 levels was to be 43%[11]. The sample was calculated to be 22. We were able to collect a sample of 33 patients with help of non-probability consecutive sampling after application of criteria furnished. All the new patients of chronic diarrhoea[12] of ages between 12-65 years who had low serum vitamin B 12 (serum cobalamin) levels (<118 picogram per liter and normal serum folate levels (between 3 to 16 nanogram per liter)[13]were included in the study. Patients who were already on treatment for diarrhoea due to irritable bowel syndrome, chrons disease, ulcerative cholitis, celiac disease, lactulose intolerance, malabsorption syndromes, and chronic infections were excluded. The patients with iron deficiency anaemia, rectal bleeding, abdominal pain, elevated erythrocyte sedimentation rate, diabetes mellitus, hypertension, deranged thyroid profile, electrolyte imbalance, hypoalbunemia and deranged liver or kidney function tests were also excluded from the study. Patients on drugs like Metformin and lactulose and pregnant ladies were excluded from the study.

All the patients were booked from Medicine and Allied outpatient department by non-probability consecutive sampling. The patients were apprised about the study protocol and follow-up period of up to three months. The patients who agreed to participate were recruited after written informed consent. The patients recruited in the study were subjected to thorough work-up including detailed histories, laboratory investigations and physical examination including cardiac, pulmonary, abdominal and neurological examination. The demographic details of patients including gender, age, weight, BMI and history of fatigue and weight loss were recorded Vitamin B12 (Injection neurobion, Merck Ltd) was started in all patients with low vitamin B12 levels. 1000 micrograms per millimetre was given as deep intramuscular injection in thickest part of deltoid muscle with help of a 5 cc syringe (B.Braun) every day for seven consecutive days followed by maintenance dose which included 1000 micrograms as intramuscular injection per month for three months.[14] Patients were called for follow-up. If diarrhoea settled patients were given the option of telephonic follow-up and were advised Vitamin B12 levels at 2 weeks, 3 months and 6 months and they were asked for any recurrence of diarrhoea between 7 days to 6 months. However, if diarrhoea did not settle within a week, patients were subjected to further evaluation. The sub-set of patients in whom diarrhoea was settled were followed up till three months and patients who lost to follow up were excluded. The efficacy was defined as settlement of diarrhoea with parenteral vitamin B12 within one week. Recurrence of diarrhoea was any episode of diarrhoea during treatment and follow-up period. The secondary outcomes were adequacy of serum vitamin B12 levels at 2 weeks and three months and frequency of recurrence. The study protocol has been summarized in Figure-1.

The data was statistically analyzed using SPSS-26. Frequency & percentages of qualitative variables determined. For quantitative variables, means and standard deviations were computed. The statistical tests employed were T-test and chi-square analysis.

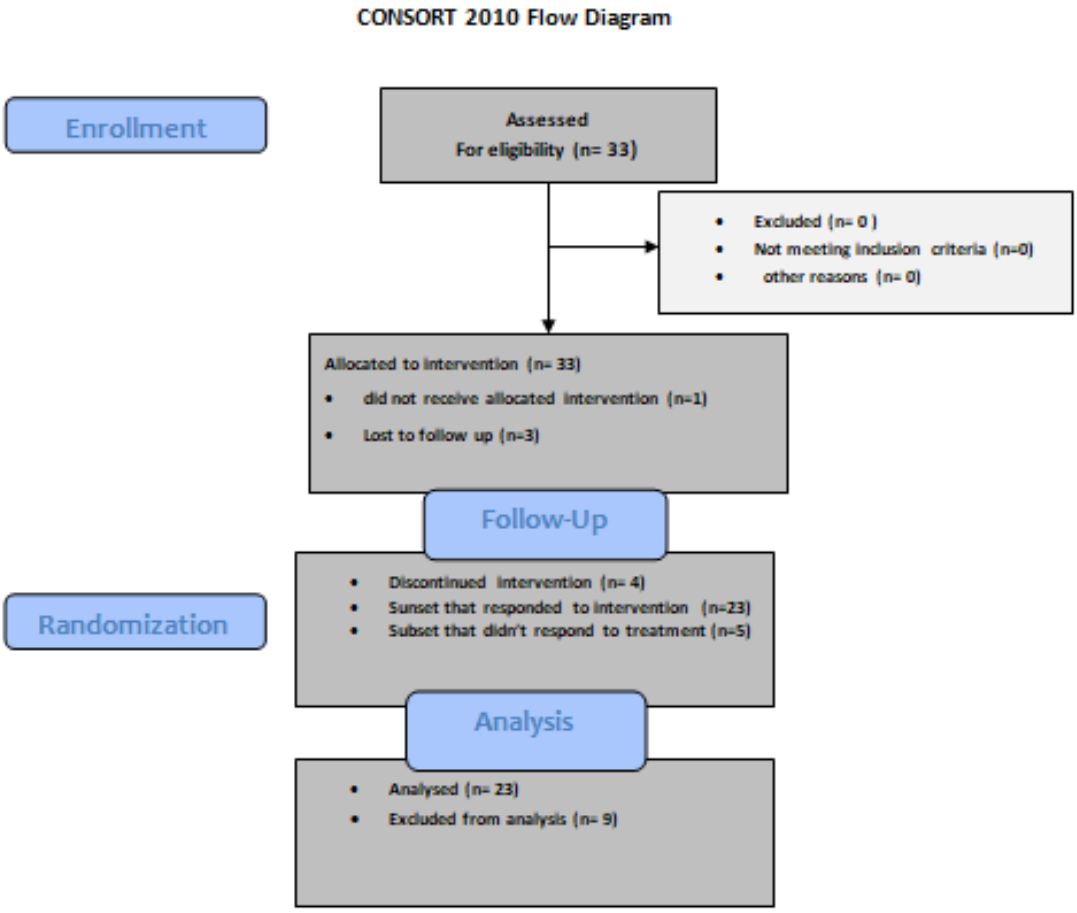

Figure-1

RESULTS

Out of thirty-three patients who were recruited in the study, twenty-nine patients followed the study protocol. Three patients lost to follow up and one patient did not show compliance to the treatment, therefore, these four patients were dropped from final results. The primary outcome was efficacy of vitamin B12 treatment that is settlement of diarrhoea after B12 supplementation.

The mean age of the patients in the study group was 39.72±11.65 years, mean weight of patients was 69.03±5.30 kilograms and mean height was 158.97±6.06 centimetres. The mean Basal mass index calculated on the basis of anthropometric measures of weight and height was 27.14±2.42 kg/m^2. The mean baseline vitamin B12 levels at start of stud were 95.28±5.54 pg/L which was quite low. There were total 19 (65.5%) males and 10 (34.5%) females in the group. There were 9 (31.0%) patients who gave history of weight loss and 20(69.0%) patients believed that their weight was stable despite diarrhoea. Fatigue was a symptom present in 19(65.5%) patients and 10 (34.5%) patients did not have fatigue. All the demographic variables are presented in Table-1.

Efficacy of parenteral B12 supplementation was seen in 23 (79.3) patients. Five (20.7) patients' diarrhoea was not relieved within a week therefore they were subjected to further evaluation and treatment and they were excluded from follow-up at 2 weeks and 3 months. Out of twenty-three patients who responded to vitamin B12 supplementation, 14 (48.3) patients showed improvement in less than two days 6 (20.7) showed improvement in less than four days and 1 (3.4) patient stopped experiencing diarrhoea within seven days of intramuscular vitamin B12 with *p*-value of <0.001. The twenty-three patients who responded to vitamin B12 supplementation stayed compliant to the treatment and followed up still three months. Their serum vitamin B12 levels were measured at 2 weeks and 3 months. All 23(79.3) patients showed normal B12 levels till three months of supplementation with p value of <0.001. When enquired regarding recurrence of diarrhoea, one (4.8%) patient came with positive response but he had a single episode of diarrhoea which had no statistical significance (*p*-value <0.001). The outcomes are presented in Table-2.

Table-1: The descriptive statistics & demographics of the study group (n=29)

Parameters		**Mean±Std. Deviation**
Mean age (years)		39.72±11.65
Mean weight (kilograms)		69.03±5.30
Mean height (centimetre)		158.97±6.06
Mean BMI (kilogram/meter^2)		27.40±2.44
B12 levels before treatment (picogram/Liter)		95.28±5.54
Haemoglobin level (Grams/decilitre**)**	Male	12.48±0.93
	Female	9.43±1.27
Mean corpuscular volume (MCV) (Femtoliter**)**	Male	107.81±5.35
	Female	109.90±6.36
		Frequency (%)
Gender	Male	19(65.5)
	Female	10(34.5)
Weight Loss	Yes	9(31.0)
	No	20(69.0)
Fatigue	Yes	19(65.5)
	No	10(34.5)

Table-2: The primary & secondary outcomes of the study group (n=29)

		Yes Frequency n (%)	**No Frequency n n (%)**	***p*-value**
Efficacy		23 (79.3)	5 (20.7)	<0.001
Recurrence of diarrhoea		1 (3.4)	22 (75.9)	<0.001
		Frequency (%)		
Time lapse between Supplementation and relieve of diarrhoea	**<2 days**	14 (48.3)		<0.001
	<4 days	6 (20.7)		
	<7days	1 (3.4)		
		Normal Frequency n (%)	**Abnormal Frequency n (%)**	
B12 levels after 2 weeks of supplementation		23 (79.3)	0 (0)	<0.001
B12 levels after 3 months of supplementation		23 (79.3)	0 (0)	<0.001

DISCUSSION

A statistically significant number of patients responded to vitamin B12 supplementation which reinforced the fact that chronic diarrhoea responded to vitamin B12 treatment. We gave vitamin B12 supplementation to patients with intractable diarrhoea that has no associated red flag signs and symptoms. The sub-group of patients who responded with in one week of parenteral therapy was followed up to three months to avoid any ethical conflicts. Therefore, we did not have a definite control group to compare the results. However, we were able to infer those patients who had adequate levels showed substantial improvement with efficacy of greater than seventy-nine percent.

The association of vitamin B deficiency with diarrhoea was highlighted by Jagadish *et al* in a case report who found that chronic diarrhoea subsided in an infant with vitamin B12 deficiency. The other pathological conditions found in same infant were haemolytic anaemia, splenomegaly and neurological consequences like irritability and anorexia. The infant was also transfused packed cell to correct anemia.[15]

The neurological and haematological manifestations have a constant association with vitamin B12 deficiency but diarrhoea is an unusual symptom. Paraesthesia's, altered reflexes, ataxia, urinary incontinence, impaired sensory sensations, cognitive impairment and psychiatric problems have been related to vitamin B12 deficiency. The gastrointestinal pathologies are usually seen as forerunner of B12 deficiency like ilieal resection, chrons disease, and irritable bowel syndrome and so on. Diarrhoea in such conditions is a cause rather than a nutritional consequence of vitamin B12 deficiency[16].

According to Scatliff *et al*[17] diarrhoea is a negative predictor of vitamin B12 deficiency and patients with diarrhoea not liable to develop vitamin deficiencies including vitamin B12. Recently the association of diarrhoea has been established with deficiency of vitamin B12 by Esposito *et al* who demonstrated that cyanocobalamine deficiency leads to functional diarrhoea and bloating. They were not able to develop as strong association between diarrhoea and vitamin B12 deficiency as they reported diarrhoea to be a less frequent complication of cyanocobalamine deficiency.

According to another case report by Meyers *et al*[18], vitamin B12 deficiency was found in a young lady with bloody diarrhoea. She also had autoimmune gastritis, neurological symptoms and anaemia and her symptoms improved with parenteral vitamin B12. The patients in our study did not have blood in diarrhoea and other associated symptoms like nausea and vomiting. All the patients had a functional diarrhoea with significant fatigue (66%) but there was no significant weight loss (23%). The diarrhoea improved within 24 hours in almost 47 percent patients in our

study probably due to the fact that we gave parenteral cyanocobalamine instead of oral as intramuscular b12 is more efficient in treating B12 deficiency.[19]

According to Mouchaileh *et al*[20], vitamin B12 deficiency can lead to non-specific symptoms like nausea, diarrhoea and vomiting in elderly patients as these patients are at increased risk of malabsorption due to age related changes in gastrointestinal tract and presence of comorbid conditions. The high index of suspicion regarding vitamin B12 deficiency in patients with diarrhoea in this age group can lead physicians to start early parenteral treatment and prevent neurological sequel and frailty syndrome in this vulnerable population.

CONCLUSION

Replacement of vitamin B 12 in patients with chronic diarrhoea having low vitamin B 12 results in settlement of diarrhoea.

Conflict of interest: None

Limitation of study: We did not compare the efficacy to the patients who did not receive the parenteral treatment to avoid ethical conflicts. Our study was single center.

Acknowledgement: All my juniors and senior collages who helped and supported me.

Funding source: None

AUTHORS' CONTRIBUTIONS

NA, AM, JK, SB, MJ, MA**:** Drafting of work, Design analysis, Data acquisition &data interpretation, Approval of final version to be published.

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Submitted: March 1, 2024	*Revised: March 16, 2024*	*Accepted: March 25, 2024*

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