

Research Article

Feasibility of Oral Vitamin B12 Supplementation After Total Gastrectomy: Single Institution Cohort

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Abstract

Objective: Vitamin-B12 (VB12) deficiency is a severe long-term risk for patients following Total Gastrectomy (TG). The absence of intrinsic factor secretion from gastric parietal cells often mandates parenteral administration, which can be costly and inconvenient to patients. However, recent data suggests the convenient oral route of administration is just as effective. This study evaluates our group's experience with exclusive oral VB12 supplementation post-TG.

Methods: Conducted as an IRB-approved retrospective cohort analysis, the study included TG-patients treated at a tertiary cancer center from 2014 through 2021. The primary comparison was between oral and other routes of administration, with outcomes measuring postoperative serum-VB12 and hemoglobin till 3 years post-TG. Longitudinal analysis assessed possible associations between routes and patient outcomes.

Results: 52 TG-patients were identified (median age 61-years; male 54%). Most (n=43,83%) received exclusive oral-VB12, while the remaining received parenteral (IM n=6, SubQ n=1) or a combination (n=2, oral+parenteral). At 6-months, 1-year, 2-years and 3-years post-TG, 80% (n=39/49), 68% (n=30/44), 71% (n=24/34) and 50% (n=8/16) of patients, respectively, maintained complete oral supplementation. Mean-VB12 levels for oral administration were 1085 (n=16), 967 (n=19) and 1012 (n=18) pg/mL at 6-months, 1-year and 2-years, respectively. At 2-years, the mean-hemoglobin level was 12.4 (n=23) and the mean-corpuscular-volume was 90.8 (n=18), with no association between route and these two parameters.

Conclusion: Oral VB12 administration is a safe, feasible and convenient long-term supplementation route for patients after TG, however, VB12 levels need to be monitored long term.

Keywords: Vitamin B12; Gastric Cancer; Total Gastrectomy; Parenteral; Nutrition; Postoperative Care

Introduction

Gastric cancer (GC) is the 5th most diagnosed cancer worldwide and is heavily responsible for a significant portion of the cancer related mortality through the world [1]. In the West for patients clinically diagnosed with locoregional cancer, multimodality therapy with peri-operative chemotherapy and surgical resection has been defined as the standard of care [2]. Surgical resection includes the complete removal of the involved stomach along with a margin of adjacent normal tissue and surrounding lymph nodes [2,3]. To this end, Total Gastrectomy (TG) is necessary for some patients [2,4]. Additionally, TG may be utilized in patients with a diagnosis of hereditary diffuse gastric cancer syndrome/Pathogenic CDH-1 gene mutation as a prophylactic procedure for the prevention of the subsequent development of GC [5,6]. However, without the stomach, the body is absent of parietal cells which are responsible for the production of the glycoprotein Intrinsic Factor (IF) which facilitates the binding of cobalamin known as Vitamin B12 (VB12) and the formation of the vitamin-protein complex. Consequently, the IF-VB12 complex binds to receptors within the ileal mucosa for absorption into the portal circulation for bioavailability [7,8]. Therefore, VB12 deficiency could be a life-threatening complication for patients undergoing TG [9]. VB12 deficiency can manifest with neurologic and

hematologic complications, including the development of neuropathy, dementia and megaloblastic anemia [7-13]. Lifelong supplementation of VB12 is, therefore, necessary in patients who undergo a TG to prevent the development of these devastating complications [9,13].

Historically, it was believed that only parenteral routes such as intramuscular, subcutaneously, sublingually or intranasally were effective to supplement this vitamin as the lack of IF made the oral route ineffective [13,14]. However, a few recent studies have shown that the oral route of VB12 supplementation is a practical and safe alternative to the parenteral routes with a proposed mechanism of action of passive absorption of VB12 in the bowel [15,16]. Despite these recent advances, orally administered VB12 supplementation is not yet standard for patients post TG. Over the last few years, patients' post-TG at our institution have been recommended to receive exclusive oral supplementation of VB12. With this study, we aim to assess the effectiveness of this practice and the long-term changes in the routes of supplementation.

Methods

An Institutional Review Board (IRB) approved review was conducted retrospectively at Moffitt Cancer Center using an institutionally maintained database. Patients who underwent a Robotic assisted Total Gastrectomy (RTG) with Roux-en-Y reconstruction between 2014 and 2021 were selected. Patient demographics, clinical, pathological and cancer treatments were recorded for analysis. Intra-operative factors such as surgical techniques, blood loss, duration of procedure and utilization of feeding jejunostomy tube for subsequent nutritional support were evaluated. Technically all patients received a circular stapled esophago-jejunal anastomosis, the roux-limb was measured at 55 cm. The initial route of VB12 administration was abstracted from the Electronic Medical Record (EMR) and classified as oral versus parenteral. Any changes in the route of administration and dosages were additionally abstracted and recorded. Biometric and nutritional data such as weight (kg) and BMI were collected. Biochemical data including serum VB12 levels, Hemoglobin (Hgb), Hematocrit (Hct) and Mean Corpuscular Volume (MCV) were recorded. Biochemical results were then compared stratified by route of VB12 supplementation. Descriptive statistical procedures were conducted and presented to assess the frequency in addition to the related percentages for each route. Mean, median and mode values were also calculated for the dosages related to each respective route of administration of the VB12 replacement therapy. Longitudinal analysis was performed using a linear regression model in order to analyse the strength of association between the oral route of supplementation and the VB12 biomarkers of interest. A p-value less than 0.05 was considered statistically significant. Statistical analyses were performed using the IBM Statistical Package for Social Sciences (SPSS) software platform version 29 (Chicago, IL). Longitudinal analyses were performed using Stata version 14 (College Station, TX). Finally, we describe the changes in route of administration over time using R programming studio version 4.4.1 (Vienna, Austria) for further statistical computing through graphical analysis.

Results

Patient Data

From 2014 to 2021, 52 patients underwent RTG. Characteristics of the cohort are shown in Table 1. The median age was 61 years (range 29-79). Most patients were male (54%). Forty-three (n=43, 83%) patients had a cancer diagnosis, 8 (15%) patients were treated for hereditary GC syndrome prophylaxis and 1 (2%) was diagnosed with bleeding Familial Juvenile Polyposis. Of the patients with a cancer diagnosis, 23/43 (53%) had clinical stage III disease. Neoadjuvant therapy was utilized for 39 of the 43 patients who had a diagnosis of gastric carcinoma (Table 1). Feeding jejunostomy tube was utilized in 44 (85%) of patients for early postoperative nutritional support.

VB12 Supplementation Route

Oral supplementation alone was started in 43 (83%) after surgery, two patients received Intramuscular (IM) VB12 in combination with oral supplementation (4%), 6 (12%) of the remaining patients preferred IM and 1 (2%) preferred subcutaneous (SubQ) administration. Table 2 demonstrates the distribution of patients receiving each route of administration over different time points up to three years post-TG. Oral VB12 route of administration remained the most common method of supplementation during follow up, with 68% (n=30/44) at 1 year, 70% at 2 years (n=24/34) and 50% (n=8/16) at 3 years post-TG.

At 6 months, 4 patients who had initially received complete oral VB12 supplementation were transitioned to combined routes, by their local providers. At 1 year 4 additional patients were transitioned from complete oral VB12 to parenteral supplementation (3 IM and 1 SQ), by their local providers and one transitioned from combined (Oral/Sublingual) to sublingual. At 2 years no

additional patients were transition to parenteral supplementation, but one patient transitioned back from Combined (Oral/IM) to oral only. At year 3, three additional patients were transition to parenteral supplementation and two to combined supplementation.

VB12 Deficiency Surveillance

In longitudinal analysis utilizing linear regression, there was no association between initial oral B12 supplementation route and either postoperative serum B12 level ($p=0.55$) or postoperative hemoglobin level ($p=0.48$). All patients maintained a serum VB12 level above the threshold constituting deficiency over the course of their post operative follow up, regardless of route of supplemental VB12 administration (Fig. 1). Patients with oral administration maintained stable mean levels with minimal fluctuation over the follow up: among patients with complete oral supplementation and available data, the average serum B12 level was 1084 pg/mL at 6 months ($n=16$), 967 pg/mL at 1 year ($n=19$) and 1012 pg/ml at 2 years ($n=18$) as indicated in Table 3. Serum VB12 levels were infrequently checked for patients receiving parenteral supplementation.

Similarly, there was no significant association between Hgb concentration and oral VB12 supplementation route (linear regression, $p=0.48$). Among the patients with complete oral administration, the mean hemoglobin levels 1 year and 2 years post operation were 12.3 and 12.5, respectively. However, it is imperative to recognize that some patients received oncologic therapies at different points in their follow up (Fig. 2).

We were unable to report on symptomatic peripheral neuropathy as a result of VB12 deficiency due to overlapping symptoms between chemotherapy induced neuropathy. However, it was observed that none of the 9 patients who did not receive chemotherapy had complaints of neuropathy, while some neuropathy symptoms were universally reported among patients receiving chemotherapy. No further analysis was performed given statistical limitations.

Demographics	Overall (n=52)
Age, years median (range)	61 (29-79)
Male	54%
BMI at diagnosis (mean)	27.5(5)
Weight at diagnosis Kg (SD)	81.9(SD 18.5)
Pathologic details	
Histologic Diagnosis	
Adenocarcinoma	43 (83%)
Hereditary diffuse cancer	8 (15%)
Familial Polyposis	1 (2)
Clinical Stage (%)	
c0	1 (2)
cI	4 (9)
cII	13 (30)
cIII	23 (54)
cIV	2 (5)
Neoadjuvant Therapy (%)	43
Chemotherapy	39 (91%)
Radiation	13 (30%)
None	4 (9%)

Table 1: Patients' characteristics.

n	Post op (52)	6M (49)	1Y (44)	2Y (34)	3Y (16)
Oral	43	39	30	24	8
Sublingual		1	1	1	
Parenteral IM	7	5	9	6	4
SQ	6	4	8	4	3
	1	1	2	2	1
Combination Oral/Sublingual/IM	2	4	3	3	4
M=Months, Y=Years					

Table 2: VB12 supplementation route over time.

Laboratory Marker	Route	6 months	12 months	24 months
Serum VB12 (pg/ml)	Oral	1084 (n=16)	967 (n=19)	1012 (n=18)
	IM	848 (n=4)	679 (n=5)	766 (n=5)
	SubQ	266 (n=1)	924 (n=1)	
	Combined	967 (n=3)	679 (n=6)	1004 (n=4)
Hemoglobin (g/dl)	Oral	11.74 (n=22)	12.29 (n=29)	12.48 (n=23)
	IM	12.86 (n=5)	13.3 (n=6)	12.3 (n=5)
	SubQ	11.5 (n=1)	9.7 (n=1)	9.3 (n=1)
	Combined	13.2 (n=3)	13.37 (n=6)	12.28 (n=5)
MCV (fl)	Oral	90.65 (n=26)	89.36 (n=25)	90.15 (n=18)
	IM	95.03 (n=8)	91.12 (n=5)	95.64 (n=5)
	SubQ	82.7 (n=1)	82.4 (n=1)	80.4 (n=1)
	Combined	94 (n=4)	89.83 (n=6)	93.6 (n=4)

Table 3: Mean laboratory results by route over time.

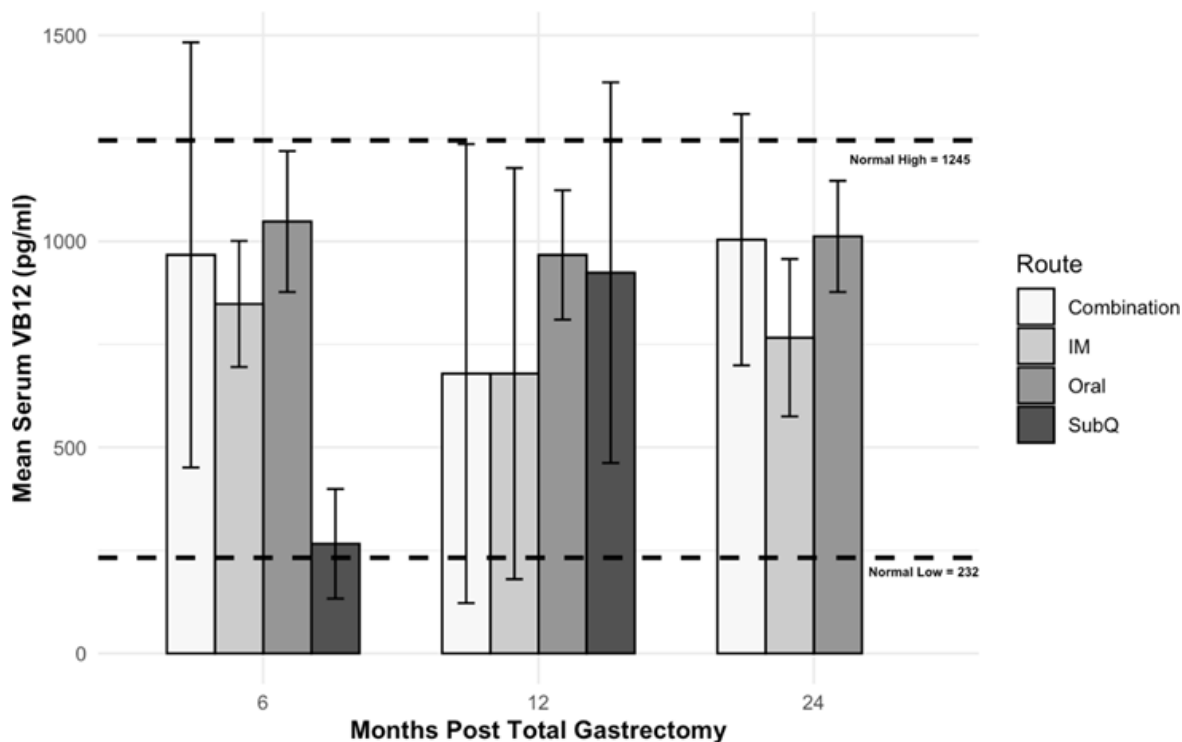


Figure 1: Bar graphs of the mean serum VB12 levels over the follow up period are displayed relative to each administration route. Error bars represent 95% confidence interval. Combination: oral + parenteral; IM: intramuscular; SubQ: subcutaneous.

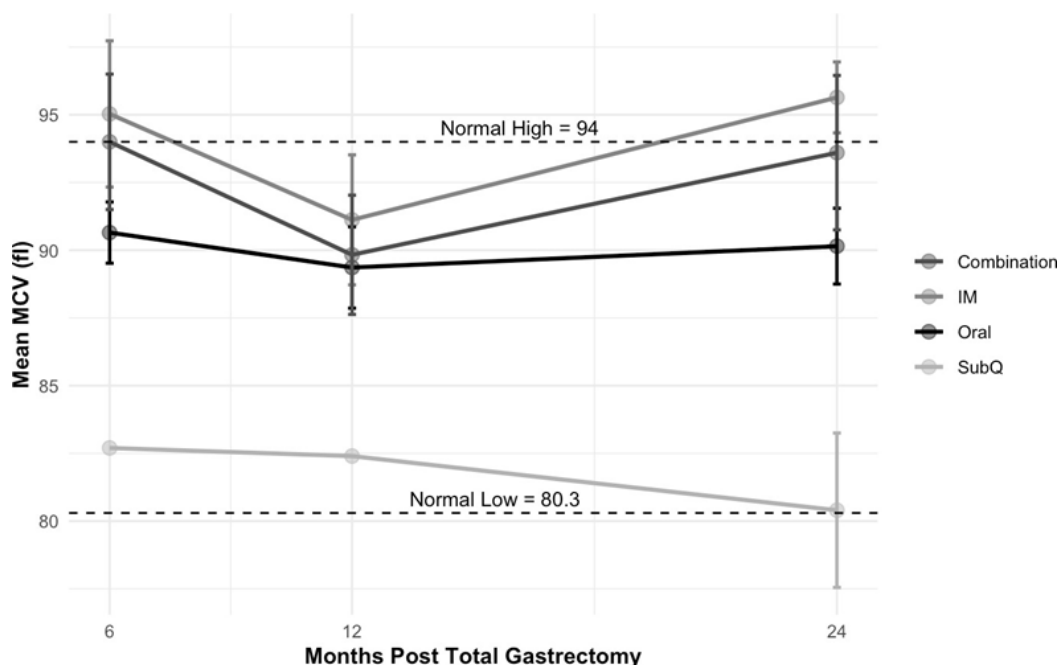


Figure 2: Line graph of the average mean corpuscular volumes over the follow up period are displayed relative to each administration route. Error bars represent 95% confidence interval. Combination: oral + parenteral; IM: intramuscular; SubQ: subcutaneous.

Discussion

Long term survival after major oncologic surgery continues to improve with more effective multimodality therapy, this is evident for patients diagnosed with GC and undergoing TG, survival is also prolonged for patients undergoing prophylactic TG. Focusing on the management and prevention of long-term complications for these patients is fundamental [9,16]. In this context, Vitamin B12 supplementation is a relatively simple and necessary intervention for all patients post TG to prevent subsequent development of symptoms [13]. Historically, parenteral VB12 supplementation was thought to be required, however, over the last 20 years there has been recognition that the oral route could be an alternative for these patients and despite more recent series supporting the safety and effectiveness of this route, its universal adoption has been very limited [15,16]. In this context a few years back in our institution we began to recommend exclusive oral supplementation for most of our RTG patients within the first post-operative month or when deemed safe to proceed with oral intake at dosages of 2000 to 3000 µg by a gummy supplement daily. We measured the VB12 serum levels and adjusted dosing with a goal of >400 (pg/ml). However, overtime there were gradual transitions toward the more usual parenteral and sublingual routes of administration, as the oncologic follow up was less intense and patients returned to be management by their PCPs and local oncologists. We do not know if these changes were a result of the patient's uneasiness about the efficacy of the oral form, if the other medical providers expressed concern about the oral VB12 effectiveness or the belief that a VB12 supplementation may be associated with increased energy [17].

At the 1-,2- and 3-year time points, more than 50% of patients continued to use the oral route as the only source of supplementation of VB12, displayed in Table 2. Moreover, serum VB12 concentration, hemoglobin and median corpuscular volume did not correlate with the corresponding VB12 route of supplementation, this is likely the result of adjustments to the dose given to patients based on their measured VB12 levels. These findings contribute to the literature supporting the safety of complete oral supplementations of VB12 after TG.

Our limitations are related with the fact that this is a single institution series, with most patients having diagnosis of cancer, allowing for the possibility of bias in selecting which patients would remain receiving only enteral route and maybe the more infirm patients or patients undergoing chemotherapy receiving parenteral route. Additionally, these patients had intense oncologic follow up, suggesting that this approach may not work for patients in the community after oncologic care is concluded, as there may be need for periodic serum VB12 measurements with complete oral administration. Additionally, some patients did not have the intense VB12 measurements by the oncologic providers or were lost to follow up or succumb to their oncologic process limiting what can be said about the success of long-term exclusive oral VB12 supplementation.

Conclusion

Long-term exclusive oral supplementation of VB12 can be a safe, effective and convenient strategy for patients undergoing total gastrectomy. Continual monitoring of serum levels can dictate the appropriate dosages utilized.

Conflict of Interest

The authors report no conflict of interest that may be interpreted as influencing the research.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author JP upon reasonable request.

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