VITAMIN B

RECOMMENDATION

We suggest against the use of B vitamins as adjunct in the treatment of patients with COVID-19. *(Very low quality of evidence; Conditional recommendation)*

Consensus Issues

Vitamin B plays an important role in cell functioning and boosting the immune system. Therefore, there is a need to assess the potential of Vitamin B as an adjunct treatment for COVID-19.

There were no studies that assessed the use of Vitamin B alone as an adjunct treatment for COVID-19 but there are still ongoing studies that can provide a clear picture on the use of Vitamin B as adjunct treatment. There were also no studies found that assessed the correlation of Vitamin B deficiency and cytokine storm. However, a prospective study that investigated the levels of Vitamin B12 and folate plasma level among patients admitted for COVID-19 pneumonia until they were transferred to ICU or death ensued suggested that there was a potential association between high plasma levels of Vitamin B12 and increased risk of mortality.

EVIDENCE SUMMARY

Should B Vitamins be used as an adjunct in the treatment of COVID-19?

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Key Findings

There is one cohort study on the use of vitamin D/magnesium/vitamin B12 (DMB) supplementation on patients with COVID-19 infection. Likelihood of subsequent oxygen therapy including ICU support was significantly less for those taking DMB. However, there was no significant difference when looking at oxygen therapy alone or ICU support alone. There were no adverse events directly attributed to DMB use in the cohort study. There is very low certainty of evidence that suggests an association between excessive levels of Vitamin B12 and poorer outcomes in COVID-19 patients. Overall, there is very low certainty of evidence due to risk of bias based on the observational design, as well as issues with directness (DMB was given in combination with vitamin D and magnesium) and imprecision (due to limited sample size).

Introduction

The B vitamins are as follows: B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid), B6 (pyridoxine), B7 (biotin), B9 (folic acid) and B12 (cobalamin). When all these are combined, they are referred to as vitamin B complex [1].

These water-soluble vitamins contribute to cell functioning and energy metabolism to create and maintain healthy cells thus playing a major role in the body's immune system [2]. For instance, while vitamin B1 has some anti-inflammatory effects, vitamin B6 plays a role in T cell production, and vitamins B3 and B12 affect the immune system [3,4]. This combined boost to the immune system is hoped to translate to beneficial effects when B vitamins are taken as an adjunct for COVID-19 treatment [4].

Review Methods

We conducted a search using Medline, Cochrane Central and Google Scholar using a combined MeSH and free text search on B vitamins – B1, B2, B3, B5, B6, B7, B9, B12 - including riboflavin, thiamine, niacin, niacinamide, pantothenic acid, pyridoxine, pyridoxal, pyridoxamine, biotin, folic acid, hydroxocobalamin, mecobalamin, transcobalamins, cyanocobalamin, cobamides, vitamin B complex and coronavirus, COVID-19, SARS-CoV-2, or NCOV. We looked for randomized controlled trials (RCT) and if there were no RCTs, proceeded to search for observational studies.

Results

Efficacy

As of this date we found no randomized controlled trials on the use of B vitamins as adjunctive treatment on patients with COVID-19. There was, however, the cohort study of Tan et al. in Singapore, that compared patients given a short course of vitamin D/magnesium/vitamin B12 supplements (DMB) upon diagnosis of COVID-19 to those who were not given DMB [5]. This study included 43 consecutive patients who were SARS-CoV-2 positive by polymerase chain reaction (PCR) from nasopharyngeal or throat swab. The DMB was started on all consecutive patients who were above 50 years of age not requiring oxygen therapy, ICU support, or any of the two. The regimen consisted of a single daily oral 1000-IU dose of vitamin D3 (colecalciferol), 150 mg of magnesium oxide, and 500 µg vitamin B12 (methylcobalamine) for ≤14 days. All those who were not given DMB at that time served as control group. The authors defined primary outcome as the requirement of oxygen therapy when oxygen saturation by pulse oximetry fell < 95%, intensive care unit (ICU) support, or both.

Results showed that fewer patients receiving DMB actually required subsequent oxygen therapy plus ICU support compared to controls, with an odds ratio (OR) of 0.13 (95% CI 0.03, 0.59). No significant difference was seen for the outcomes of 1) requiring oxygen therapy with no ICU support [OR 0.3 (95% CI 0.06, 1.63)] and 2) requiring ICU support alone [OR 0.14 (95% CI 0.02, 1.25)]. Multivariate analysis also showed that DMB remained a significant protective factor after adjusting for age [OR=0.195 (95% CI 0.041, 0.926)] and hypertension [OR=0.182 (95% CI 0.038, 0.859)]. They also did a subgroup analysis, removing patients < 60 years of age with diabetes, but the analysis of the primary outcome did not show any significant difference because of the limited sample size.

This study had issues on risk of bias because of its observational design. There was also downgrading on directness because the study did not look at the effect of B vitamin alone since it was given in combination with vitamin D and magnesium. The limited sample size, leading to imprecision, also contributed to the downgrading of the quality. At best, the certainty of evidence for the use of vitamin B as adjunct for the treatment of COVID-19 patients is very low.

Safety

Tan et al. reported that there were no side effects or adverse events with the use of DBM in their cohort study. There was also no death reported in the follow-up period [5].

The study of Dalbeni et al. investigated the levels of vitamin B12 and folate plasma level in patients admitted for COVID Pneumonia, who they followed prospectively until the outcome of transfer to ICU or death ensued [6]. Out of 49 patients, nine had the outcome: these patients were significantly older (p = 0.01), had lower P/F ratio (p = 0.01) and higher plasma level of B12 (p = 0.02) compared with those who recovered. On multivariate analysis, however, only age was independently associated with a worse outcome (β±SEM 0.016 ± 0.005, p = 0.001). However, the study suggested a potential association between high plasma levels of vitamin B12 and increased risk of mortality, citing also previous literature where excessive vitamin B12 levels were associated with the same, in both the general population [7] and ICU patients [8].

Hypervitaminosis B6 due to excessive self-medication has been known to cause peripheral neuropathy with both motor and sensory deficits [9,10].

Recommendations from Other Groups

The NIH Covid-19 Guidelines does not mention the use of B vitamins as supplement to COVID-19 treatment [11]. The Australian Guidelines for the clinical care of COVID-19, the Surviving Sepsis Campaign Guidelines on COVID-19, and the Infectious Disease Society of America (IDSA) on the Treatment and Management of Patients with COVID-19 were also silent with regard to B vitamin use [12-14].

Research Gaps

There is no evidence yet on the efficacy of B complex vitamins in the following settings: 1) when used as the sole adjunct to standard therapy, 2) patients with COVID-19 who have normal versus deficient vitamin B levels, and 3) patients across various ages and comorbid conditions.

There are currently four ongoing randomized controlled trials listed in *ClinicalTrials.gov* on the use of B vitamins in COVID-19 patients [15]. There is one registered and published protocol of a randomized controlled trial on the impact of various vitamins including vitamin B on improvement and mortality rate in ICU patients with COVID-19 listed in Cochrane Central Register of Controlled Trials, whose corresponding author we reached out to, for the results of the study which should have completed recruitment in July 2020 [16]. This evidence summary will be updated as soon as those studies come out and confirmed eligible for inclusion.

References

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Appendix 1. Characteristics of Included Studies

Study ID	Patients (n)	Interventions	Outcomes	Method
Tan 2020	All consecutive COVID-19 patients ≥50 years of age admitted to a tertiary hospital. Must be positive for severe acute respiratory syndrome coronavirus (SARS-CoV)-2 polymerase chain reaction (PCR) from nasopharyngeal or throat swab. n = 43	1000-IU dose of vitamin D3 (colecalciferol), 150 mg of magnesium oxide, and 500 mg vitamin B12 (methylcobalamine) for 14 days given per orem once a day compared to usual care/standard care at that time (Jan 15 to April 15, 2020)	Primary outcome was requirement of oxygen therapy when oxygen saturation fell <95% detected by pulse oximetry, intensive care unit (ICU) support, or both	Cohort (non-randomized, observational)

Appendix 2. GRADE Evidence Profile

Author(s): Sulit, Maria Vanessa; Villarta-de Dios, Namnama
Question: Vitamin B Supplements compared to Standard Care or Placebo for COVID-19
Setting: In-hospital
Bibliography: Tan CW, Pock L, Kalimuddin S, Cherng BPZ, Teh YE, Thien SW et al. Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B12 in combination on progression to severe outcomes in older patients with coronavirus (COVID-19). Nutrition. 2020; 79-80. https://doi.org/10.1016/j.nut.2020.111017

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin B Supplements	Standard Care or Placebo	Relative (95% CI)	Absolute (95% CI)		
Requiring O2 therapy including ICU support (follow up: range 1 to 14 days)												
1	observational studies	very serious [a]	not serious	serious [b]	serious [c]	all plausible residual confounding would reduce the demonstrated effect	3/17 (17.6%)	16/26 (61.5%)	**OR 0.13** (0.03 to 0.59)	**443 fewer per 1,000** (from 570 fewer to 130 fewer)	⨁◯◯◯ VERY LOW	
Requiring O2 therapy without ICU support (follow up: range 1 to 14 days)												
1	observational studies	very serious [a]	not serious	serious [b]	serious [c]	all plausible residual confounding would reduce the demonstrated effect	2/17 (11.8%)	8/26 (30.8%)	**OR 0.30** (0.06 to 1.63)	**190 fewer per 1,000** (from 282 fewer to 112 more)	⨁◯◯◯ VERY LOW	
Requiring ICU support (follow up: range 1 to 14 days)												
1	observational studies	very serious [a]	not serious	serious [b]	serious [c]	all plausible residual confounding would reduce the demonstrated effect	1/17 (5.9%)	8/18 (44.4%)	**OR 0.14** (0.02 to 1.25)	**344 fewer per 1,000** (from 429 fewer to 56 more)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. This was a non-randomized, cohort study.
b. Vitamin B12 was taken in combination with vitamin D and magnesium
c. Sample size was limited to 17 patients in the DMB group and 26 patients in the control group.

Appendix 3. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
Impact of vitamins A, B, C, D, and e supplementation on improvement and mortality rate in ICU patients with coronavirus-19	20-60 years old with clinical or definitive diagnosis of COVID-19 by PCR test	Vitamin A, Vitamin D, Vitamin E, Vitamin C is taken four times per day B vitamins are taken as a daily Soluvit [which included thiamine nitrate, sodium riboflavin phosphate, nicotinamide, pyridoxine hydrochloride, sodium pantothenate, sodium ascorbate, biotin, folic acid, and cyanocobalamin. The control group will not receive any supplements or placebo.	Weight, height, and BMI 2; Severity of pulmonary involvement according to CT scan; Respiratory support (invasive or non-invasive); Percentage of oxygen saturation (SpO2 level); Serum levels of WBC, CRP, ESR, IL6, IFN-G, and TNF-α 6; patient's body temperature; presence or absence of involvement of organs other than the lungs (e.g., heart, liver, kidneys); duration of hospitalization; Mortality rate	Randomized; parallel assignment with concealed allocation
Improvement of the Nutritional Status Regarding Nicotinamide (Vitamin B3) and the Disease Course of COVID-19	18 years and older with SARS-CoV-2 infection confirmed by laboratory findings n = 840	1,000 mg nicotinamide [1x 500-mg conventional nicotinamide tablet and 1x 500-mg tablet with controlled-ileocolonic-release nicotinamide (CICR-NAM)] for 4 weeks versus matching placebo capsules taken daily	Frequency of: - complete symptom resolution after 2 weeks - complete symptom resolution after 4 weeks - freedom from fatigue after 2 weeks - severe COVID-19 (examination in an emergency department / hospitalisation with requirement for oxygen (at least 24 h), intensive care or ventilation / death by COVID-19) Time from diagnosis to complete symptom resolution [days]	Randomized; parallel assignment with masking

Study Title	Patients (n)	Interventions	Outcomes	Method
Effects of Nicotinamide Riboside on the Clinical Outcome of Covid-19 in the Elderly. A Randomized Double-blind, Placebo-controlled Trial of Nicotinamide Riboside NR-COVID19	70 years and older diagnosed with COVID-19 n = 100	1 g of nicotinamide riboside versus placebo orally every morning for 14 days	- Hypoxic respiratory failure - Mortality - Sepsis - Circulatory failure - Days in hospital - NAD levels	Randomized; parallel assignment with masking
Clinical Trial of Niagen to Examine Recovery in People With Persistent Cognitive and Physical Symptoms After COVID-19 Illness (Long-COVID)	18-65 years old with COVID-19 sequelae and cognitive symptoms n = 100	Niagen (nicotinamide riboside or Truniagen or vitamin B3) versus placebo capsules taken daily	Examine the effect of Niagen on/in: - cognitive functioning as measured by executive functioning and memory composite scores - depression symptoms - in anxiety symptoms - in COVID- related physical symptoms	Randomized; parallel assignment with masking
Efficacy of Micronutrient Dietary Supplementation in Reducing Hospital Admissions for COVID-19: A Double-blind, Placebo-controlled, Randomized Clinical Trial	45 – 80 years old with symptoms compatible with COVID-19: cough and fever who not fulfil criteria of hospitalization and will be in outpatient care; Positive polymerase chain reaction (PCR) or transcription-mediated amplification (TMA) test or rapid antigen test for severe acute respiratory syndrome Corona Virus-2 (SARS-	Tablet containing: ● Retinol (Vitamin A) 700 mcg ● Cholecalciferol (Vitamin D3) 10 mcg ● Alpha-Tocopherol (Vitamin E) 45 mg ● Ascorbic acid (vitamin C) 1000 mg ● Pyridoxine (Vitamin B6) 6.5 mg ● Cyanocobalamin (Vitamin B12) 9.6 mg ● Folic acid 400 mg ● Iron 5 mg ● Zinc 10 mg	- Need for hospital admission - Micronutrient basal status[SEP] - Micronutrient status at hospital admission - Micronutrient status at end of study - Inflammatory parameters - Thromboembolic disease - Oxygen supplementation[SEP] - High-Flow oxygen supplementation	Randomized; parallel assignment with masking

Study Title	Patients (n)	Interventions	Outcomes	Method
	CoV-2) or diagnostic test available	● Selenium 110 mg ● Copper 0.9 mg ● Excipients versus effervescent placebo tablet taken daily	- Invasive mechanical ventilation - Tracheostomy and more…	