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Review article

Vitamin B12 Pharmaconutrition for COVID-19

Farmaconutrición de la vitamina B12 para COVID-19

Farmaconutrição da vitamina B12 para COVID-19

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Summary

Mortality from COVID-19 disease is much greater in the elderly, many of whom succumb to acute respiratory distress syndrome (ARDS) triggered by the viral infection. High dose parenteral vitamin B12 offers a promising novel therapy for those COVID-19 patients with ARDS from sepsis / septic shock. The anti-inflammatory and antioxidant properties of vitamin B12 and transcobalamins can modulate the systemic inflammation contributing to the cytokine cascade that leads to ARDS. Clinical studies are now required to establish an appropriate regimen for administering vitamin B12 as pharmaconutrient for critically ill COVID-19 patients.

Keywords: Pharmaconutrition; COVID-19; Vitamin B12; ARDS; Critical care.

Resumen

La mortalidad por la enfermedad de COVID-19 es mayor en los ancianos, muchos de los cuales sucumben al síndrome de dificultad respiratoria aguda (SDRA) desencadenado por la infección viral. La vitamina B12 parenteral en dosis altas ofrece una nueva terapia prometedora para los pacientes con COVID-19 con SDRA por sepsis / shock séptico. Las propiedades antiinflamatorias y antioxidantes de la vitamina B12 y las transcobalaminas pueden modular la inflamación sistémica que contribuye a la cascada de citocinas que conduce al SDRA. Se requieren estudios clínicos para establecer un régimen apropiado para administrar vitamina B12 como farmaconutriente para pacientes críticamente enfermos con COVID-19.

Palabras clave: farmaconutrición, COVID-19, vitamina B12, SDRA, cuidados intensivos.

Resumo

A mortalidade pela doença de COVID-19 é muito maior em idosos, muitos dos quais sucumbem à síndrome de dificuldade respiratória aguda (SDRA) desencadeada pela infecção viral. A vitamina B12 parenteral em altas doses oferece uma nova terapia promissora para pacientes com COVID-19 com SDRA decorrente de sepse / choque séptico. As propriedades antiinflamatórias e antioxidantes da vitamina B12 e das transcobalaminas podem modular a inflamação sistêmica que contribui para a cascata de citocinas que leva à SDRA.

Estudos clínicos são necessários para estabelecer um regime apropriado para administrar vitamina B12 como um farmaconutriente para pacientes criticamente doentes com COVID-19.

Palavras-chave: farmaconutrição, COVID-19, vitamina B12, SDRA, terapia intensiva.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a global pandemic, providing one of the biggest challenges for critical care medicine. According to the World Health Organization (WHO) in June 2020 there were 10m cases and approximately 500,000 deaths worldwide, with over 40,000 in UK. Mortality has been much higher in those patients older than 70 years (25% in UK), particularly in those with pre-illness comorbidities

such as diabetes mellitus, cardiovascular disease, obesity, cancer, and chronic respiratory disease[1].

Acute respiratory distress syndrome (ARDS) is a sepsis-related process fuelled by a cytokine storm, which is triggered by a viral infection. ARDS can be severe, and life-threatening, requiring mechanical ventilation and prolonged stay in the intensive care unit (ICU) and hospital. As in other viral infections, COVID-19 patients exhibit very high levels of proinflammatory cytokines, notably interleukins 6 (IL-6), IL-1, IL-17 and tumour necrosis factor (TNF-α). The elderly and others with comorbidities have exhibited the most aggressive inflammatory response, a phenomenon that has not so far been well understood. Unfortunately, with no specific treatment for COVID-19 infection, the overall ICU mortality remains unacceptably high, at greater than 60%, underlining the urgent need for new therapeutic strategies.

Cobalamin or vitamin B12 is one of the eight essential B group water-soluble vitamins, that helps to keep red blood cells oxygenated and prevents megaloblastic anaemia. A deficiency can cause tiredness, disorientation and may be associated with cardiovascular disease and insulin resistance. Natural vitamin B12 is found almost exclusively in animal products such as fish, meat, dairy and eggs, from which the daily requirement of 2.4 microgram for adults (2.6mcg/d in pregnancy) and 1mcg/d for children is usually obtained.

B12 is absorbed in the terminal ileum where it combines with a protein, called *intrinsic factor (if)*, that is produced in the stomach. Normally only 50% of dietary B12 is absorbed, but as we age our ability to absorb B12 further decreases. Consequently, the elderly, malnourished and those who have had their colon and/or part of their terminal ileum removed, will not absorb sufficient B12 and need to supplement their diet with between 5mcg and 20mcg per day[2].

Methylcobalamin, which represents 75–90% of the body pool of circulating vitamin B12 is a reversible carrier of methyl radicals[3]. After absorption in the circulation, transport proteins, called transcobalamins (TCS) ensure B12 reaches the key enzymes in the mitochondria for lipid, carbohydrate and protein metabolism. B12-dependent enzymatic methyl group transfer is essential for protein synthesis, where removable of a methyl group from methyl folate forms homocysteine (HCYS) which is converted to methionine for de novo synthesis of a precursor of DNA. In vitro, vitamin B12 has the ability of regulating inflammatory cytokines production, inhibit intracellular peroxide production, maintain intracellular glutathione (GSH) levels, and prevent cellular apoptosis[4].

VITAMIN B12 STATUS IN THE CRITICALLY ILL

Vitamin B-12 deficiency and depletion are common worldwide, particularly among vegetarians and the elderly, being more prevalent in poorer populations. Approximately 30% of people over 60 are thought to be deficient with over 1.8 million elderly Americans estimated to be at risk of deficiency[1]. Currently there is no information on the vitamin B12 status of COVID-19 patients and no specific supplementation recommendations for critically ill patients with ARDS due to sepsis/septic shock resulting from COVID-19. However, a few data exist on the relationship between the prevalence of vitamin deficiencies and hospital mortality in the ICU. Low levels of Vitamin B12 are prevalent in patients on admission to ICU, adversely affecting up to 15% of patients older than 65 years. B12 deficiency results in haematological and neurological disorders and may be an independent risk factor for coronary artery disease[5].

An association between vitamin B12 status and inflammation in the critically ill, was demonstrated by Corcoran et al.[6], who showed that vitamin B12 levels differed between those patients who died and those who survived. Additionally, within the first 48 hours of admission to ICU, a moderate positive correlation was identified between vitamin B12 and C-reactive protein (CRP), a marker of the acute phase response. Subsequently, a second cohort trial from the same group, showed a significant relationship between vitamin B12 concentration and the *Sequential Organ Failure Assessment* (SOFA) score[7]. Thus, vitamin B12 status appears to reflect the inflammatory response, as determined by CRP during the first days of ICU stay and to be an indicator of organ failure, evaluated by SOFA score, which could be a pointer to its potential to alleviate ARDS in critically ill COVID-19 patients.

Vitamin B12 decreases significantly after cardiac surgery[8], which may be explained by its consumption for erythropoietic purposes. The phenomenon provides another example of systemic inflammation, characterized by oxidative stress with free radical generation and antioxidant depletion in the critically ill, suggesting that supplementation, could improve nutritional status after surgical insult, particularly in those patients with suboptimal dietary intake. A Spanish ICU study[9] found high prevalence of hyperhomocysteinaemia,

which is harmful for the endothelium contributing to oxidative stress, HCYS was higher in patients who received less than the recommended intake of vitamin B12 and folic acid. In contrast, adequate vitamin B12 and folic acid supplementation reduced the risk of hyperhomocysteinaemia. Further support for supplementation comes from the work of Ploder et al.[10] who observed increased total HCYS levels in non-surviving ICU patients after multiple trauma and severe sepsis, whereas HCYS levels in survivors remained stable and low. Since methionine is synthesised from HCYS via 5MeTHF in an irreversible reaction, a deficiency of B12 can trap folate in the methyl form. Thus, elevated folate concentrations can mask haematopoeic symptoms of B12 deficiency in the critically ill.

VITAMIN B12: THE INFLAMMATORY RESPONSE

In a ground-breaking hypothesis, Wheatley[11,12] has described the vitamin as a "Scarlet Pimpernel" for the potential resolution of inflammation. In effect, vitamin B12 could contribute to the aetiology of ARDS, particularly when due to infection. Experimental support for this hypothesis comes from Birch et al.[3] who elegantly demonstrated that the antioxidant properties of vitamin B12 involve reaction with reactive oxygen (ROS) and nitrogen (RNS) free radicals, exerting a GSH antioxidant sparing effect, and inducing a stress response. There is also evidence that Vitamin B12 down-regulates NF-kB levels, which may be an important signalling molecule of vitamin B12 deficiency. Additionally, methyl-cobalamin is capable of supressing interleukin-6 (IL-6) production. In human serum and cerebrospinal fluid, low levels of vitamin B12 were associated with a concomitant increase in the neurotoxic TNF-α and a decrease in epidermal growth factor (EGF). Furthermore, Weinberg et al.[13] showed that hydroxy-cobalamin (OH-B12), may play a role in modulating NOS function and NO synthesis *in vivo*. Pernicious anemia is characterized by vitamin B12 deficiency, and concomitantly low GSH levels. In sepsis/septic shock patients GSH levels drop rapidly, but vitamin B12 supplementation has a GSH sparing effect, increasing the cytosolic bioavailability of the antioxidant. This in turn promotes conversion to GSSG, generating the necessary hydrogen selenide (H_2Se) for the synthesis of selenocysteine and selenoproteins, such as glutathione peroxidise (GPx)[14]. Vitamin B12 may also play a direct role in immune defence and inflammation through a bacteriostatic function of TCS[4], which is capable of modulating the inflammatory response.

VITAMIN B12 A POTENTIAL PHARMACONUTRIENT FOR ARDS

Based on the Wheatley hypothesis and supporting animal and clinical data, the potential mechanisms by which vitamin B12 and TCS, could alleviate severe systemic inflammation leading to ARDS following severe sepsis/septic shock can be summarised as follows: by selective inhibition of iNOS and reduction of excess NO; by decreasing RNS and ROS radicals; by sparing GSH; by stimulating oxidative phosphorylation, coupled with the bacteriostatic role of TCS during phagocytosis.

Given its role as an antioxidant and an anti-inflammatory, B12 can protect against multiple organ dysfunction by modulating activity of certain cytokines, growth factors and other substrates. It follows that high dose intravenous or intramuscular injections could be used in a novel strategy against and ARDS in COVID-19 patients. However, to consider vitamin B12 as a pharmaconutrient, it will be necessary to use higher doses than those currently recommended for routine PN or EN therapy[4]. Consequently, questions regarding the optimal dose, starting time, days of treatment, and the best method of vitamin B12 administration: whether alone or in combination with other parenteral micronutrients still need to be addressed.

VITAMIN B12: SAFETY AND POSOLOGY

Adult multi vitamin products for parenteral nutrition (PN) contain 5 or 6 ug of cyanocobalamin, the stable synthetic form of B12. Standard enteral nutrition (EN) formulations contain 3-6 μg per1500 kcal/d feed, which is the daily recommended PN/EN dose[15]. Although this is about double the recommended daily intake (RDI) there is no evidence of any toxicity. Additionally, during PN there may be significant losses in the urine, as up to 25% of unbound B12 'first passes' the kidneys and B12 secreted into the bile may not be recaptured by ileal receptors if the ileum has been resected.

Vitamin B12 is relatively non-toxic in oral doses that exceed normal requirements by 10,000 fold. With a high renal excretion rate, it has been used to treat humans with cobalamin deficiency and cyanide poisoning successfully with little or no evidence of toxicity. The dose of vitamin B12 currently recommended in the *British National Formulary (BNF)*[16] for perni-

cious anaemia and other macrocytic anaemias without neurological dysfunction is 1000 μg of OH-B12 initially given intramuscularly three times each week for 2 weeks, then once every 3 months. However, in the ICU larger antidotal infusions of 5 to 15 g OH-B12 are used to treat cyanide poisoning without significant adverse effects. Current knowledge allows us to speculate that intravenous administration of 5 gram or greater doses of OH-B12, would achieve peak blood levels over 1000 micromolar with minimal side effects. Pharmacotherapy trials would need to monitor plasma and serum concentrations of total vitamin B12, methylmalonic acid, and HCYS as effective biomarkers of changes in vitamin B12 supply and metabolism[17].

CONCLUSION

Current animal and human clinical data suggest that high dose parenteral vitamin B12 may prove a promising approach for improving the antioxidant and anti-inflammatory status of COVID-19 patients with ARDS arising from sepsis/septic shock. Cobalamins could potentially be useful agents for inhibiting NOS and NO production, controlling NF-KB activation and eventual suppression, and restoring optimal bacteriostasis and phagocytosis. In this setting, vitamin B12 and/or TCS could modulate the systemic inflammation contributing to the cytokine cascade that leads to ARDS. Short-term vitamin B12 parenteral therapy comparable to the high-doses of hydroxy-cobalamin currently administered for cyanide poisoning could be safely administered. However, clinical studies are required to clarify the outstanding questions on the optimal and best tolerated dose and time of administration in critically ill COVID-19 patients with ARDS.

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Conflict of interests

The authors declare that they have no conflict of interest.

Author's contributions

GH and WM contribute equally to the article. The authors declare that they read and approved the final manuscript.

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