e-SPEN Journal 9 (2014) e76–e83

Contents lists available at ScienceDirect

e-SPEN Journal

journal homepage: http://www.elsevier.com/locate/clnu

Original article

High vitamin B12 levels are not associated with increased mortality risk for ICU patients after adjusting for liver function: A cohort study

Fiona M. Callaghan [a,*,c], Kira Leishear [b,c], Swapna Abhyankar [a], Dina Demner-Fushman [a], Clement J. McDonald [a]

[a] Lister Hill National Center for Biomedical Communications, National Library of Medicine, National Institutes of Health, 8600 Rockville Pike, Bethesda, MD 20894, USA

[b] Division of Epidemiology, Statistics, and Prevention Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, 6100 Executive Boulevard, Rockville, MD 20892, USA

ARTICLE INFO

Article history:
Received 25 September 2013
Accepted 22 January 2014

Keywords:
Vitamin B12
Critical care
Liver function
Mortality
Intensive care unit
Liver disease

SUMMARY

Background and aims: Recent research has suggested that high vitamin B12 levels may be associated with increased mortality after ICU admission. However, it is known that impaired liver function may lead to elevated B12 since B12 is metabolized through the liver, and therefore high B12 levels may serve as a proxy for poor liver function. The aim of this study is to assess the impact that liver function and liver disease have on the relationship between high vitamin B12 levels and mortality in the ICU.

Methods: We performed an observational cohort study using ICU data that were collected from patients admitted to four ICU types (medical, surgical, cardiac care and cardiac surgery recovery) in one large urban hospital from 2001 to 2008. We analyzed the medical records of 1684 adult patients (age ≥18 years) who had vitamin B12 and liver function measurements up to 14 days prior to ICU admission or within 24 h after admission.

Results: While we found an association between high B12 and mortality when we did not control for any potential confounders, after we adjusted for liver function and liver disease, no significant association existed between B12 and mortality using multivariable logistic regression (30-day mortality: OR = 1.18, 95% CI 0.81 to 1.72, $p = 0.3890$; 90-day mortality: OR = 1.20, 95% CI 0.84 to 1.71, $p = 0.3077$).

Conclusions: Elevated B12 levels are not a significant predictor of mortality after ICU admission when liver function is controlled for, and may instead be a proxy for poor liver function.

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1. Introduction

Much of the clinical research on vitamin B12 (cobalamin) has focused on B12 deficiency, but less is known about the effects of elevated B12 levels. Several studies have looked at B12 and mortality in elderly populations: some have found an association between high B12 levels and mortality[1–6] and others have not.[7,8] When studying B12, it is important to account for liver function and liver disease, as impaired liver function is known to affect B12 levels, primarily because B12 is metabolized by the liver.[9,10] Although some of the above studies did adjust for albumin (ALB),[1,4,5] none of them explicitly adjusted for a full liver function panel in a multivariable model. Lin et al.[11] found that elevated B12 levels were associated with increased mortality in hepatocellular carcinoma patients ($N = 90$). Dou et al.[12] studied $N = 149$ patients with liver failure and found that B12 levels were positively correlated with mortality after adjusting for the Model for End-stage Liver Disease (MELD) score.[13] However, neither study focused on ICU patients.

Abbreviations: ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCU, coronary care unit; CSRU, cardiac surgery recovery unit; GVIF, generalized variance inflation factor; HC, haptocorrin; ICD-9, International Classification of Disease codes, ninth revision; IQR, interquartile range; MCV, mean corpuscular volume; MELD, Model for End-stage Liver Disease; MICU, medical intensive care unit; MIMIC-II, Multiparameter Intelligent Monitoring in Intensive Care II; MMA, methylmalonic acid; PT, prothrombin time; SICU, surgical intensive care unit; TB, total bilirubin; TCII, transcobalamin II; tHcy, total homocysteine; TPN, total parenteral nutrition; VIF, variance inflation factor.

* Corresponding author. Lister Hill National Center for Biomedical Communications, National Library of Medicine, National Institutes of Health, 8600 Rockville Pike, Building 38A/9N911, Bethesda, MD 20894, USA. Tel.: +1 301 435 3199; fax: +1 301 496 0673.

E-mail addresses: Fiona.Callaghan@nih.gov (F.M. Callaghan), Kira.Leishear@nih.gov (K. Leishear), Swapna.Abhyankar@nih.gov (S. Abhyankar), Dina.Demner-Fushman@nih.gov (D. Demner-Fushman), Clement.McDonald@nih.gov (C. J. McDonald).

[c] These two authors contributed equally as Co-first authors.

2212-8263/$36.00 Published by Elsevier Ltd on behalf of European Society for Clinical Nutrition and Metabolism.
http://dx.doi.org/10.1016/j.clnme.2014.01.003

Few studies have looked at elevated vitamin B12 levels and mortality for ICU patients. Olivieri et al.[14] conducted a study of 250 elderly patients with acute myocardial infarction admitted to a cardiac care unit (CCU) and found that vitamin B12 was not a significant predictor for cardiovascular-related mortality. Corcoran et al.[15,16] studied on the effect of vitamin B12 levels on mortality in the ICU and found that there was no association between B12 deficiency and mortality, and that weak correlations existed between B12 levels, CRP, and Sequential Organ Failure Assessment (SOFA) score, a measure of acuity in the ICU.[17] Manzanares and Hardy[18] conducted a review of studies on the relationship between B12 and mortality and noted that the data on B12 and mortality for critical care patients was scarce.

In a recent study, Sviri et al.[19] examined B12 in the medical ICU (MICU), $N = 663$, and found that log B12 levels were linearly positively correlated with 90-day mortality risk after adjusting for several other factors including cirrhosis and chronic liver disease but not measures of liver function (OR 1.7, 95% CI 0.9 to 3.1, $p < 0.05$). We hypothesize that poor liver function may be the underlying cause of both the high B12 levels and increased mortality and, furthermore that B12 levels are not linearly associated with mortality risk, i.e., mortality risk may be elevated for patients with either deficient or high B12 levels. In this study, we investigate whether there is a relationship between high B12 and mortality after adjusting for liver function and liver disease.

2. Materials and methods

We performed an observational cohort study based on electronic medical records that were collected during the course of clinical ICU care and subsequently de-identified. Our study population consisted of all adult patients that had B12 values and liver function values (ALB, ALT, AST, ALP, PT, and TB) recorded in version 2.6 of the Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC-II)[20] database. MIMIC-II contains a wide variety of clinical and demographic information on approximately 24,000 adult patients 18 years or older that were admitted to the ICU at Boston's Beth Israel Deaconess Medical Center from 2001 to 2008. The database is freely available; any researcher who accepts the data use agreement and has completed human subjects training can apply for permission to access the data. We did not need patient consent as all of the data are de-identified. All of the authors have completed human subjects training, and we conducted the study under National Institutes of Health Institutional Review Board exemption number 4193.

We used lab values, including B12 values, recorded from 14 days before ICU admission up to 24 h after admission. Other variables, such as comorbidities, were based on combinations of International Classification of Diseases, ninth revision (ICD-9) diagnosis codes, which are assigned at the end of the hospital stay.

There is no consensus on the definition of high or elevated B12. Previous studies have chosen a variety of levels to represent high or very high B12 (pmol/l) levels. Some examples include: 664.2[19]; 513[1]; 700 (high) and 1500 (very high)[11]; and 601 (high) and 1000 (very high).[10] Excess B12 is either stored in the liver, present in the blood without any adverse effects, or excreted. There are no studies investigating the potential clinical effects of high B12 because, in general, there are no known adverse effects caused by elevated B12. It is probably for this reason that there is no cutoff for high B12 based on clinical outcomes. We chose a level of 1000 pmol/l because we wanted to be sure of identifying a cohort with abnormally high levels of B12 that may potentially have adverse clinical outcomes. With regard to B12 deficiency, the cut point for clinical B12 deficiency is $\leq$148 pmol/l,[21] although even the definition of deficiency is an area of debate.[22,23] We chose to categorize the B12 levels into deficient ($\leq$148 pmol/l), mid-range ($>$148 pmol/l to $\leq$1000 pmol/l), and high ($>$1000 pmol/l) groups. By doing so, we were able to estimate the mortality risk for elevated B12 compared to mid-range or deficient levels, and we did not need to make the assumption that mortality risk increases linearly with B12 levels.

We modeled two outcomes: death 30 days and 90 days after admission to the ICU. We used four groups of independent variables in our analysis: vitamin B12 category, demographics, other potential confounders, and liver disease and function. Demographic information included age at admission, gender, race, and insurance coverage. We included the following variables to adjust for liver function: ALT, AST, TB, ALP, ALB, PT, liver cancer, and non-cancerous liver disease. In general, we categorized laboratory tests using quartiles (except B12) because the laboratory values did not appear to have a linear relationship with mortality. The diagnosis of non-cancerous liver disease was defined using the following ICD-9 codes: 570 (liver necrosis), 571.5–9 (chronic liver disease and cirrhosis, excluding the 571.0–571.3 codes explicitly mentioning alcoholic liver disease as we have added alcoholism to the analysis separately), 572* (liver abscess and sequelae of chronic liver disease), and 573* (other disorders of the liver, including hepatitis and hepatopulmonary syndrome), where * indicates the group of codes that begin with that sequence. Liver cancer was defined using ICD-9 codes 155* (primary liver and intrahepatic bile duct cancer) and 197.7 (secondary liver metastases). Elevated liver function test values were not part of the definition of liver disease; liver function tests were added to the analysis separately.

We considered several other potentially confounding factors for inclusion in the final model. We used the Simplified Acute Physiology Score (SAPS)[24] – with the age component removed so we could observe the effect of age separately – in order to account for the patient's acuity during the first 24 h of the ICU stay. We considered other ICU-related factors such as first service unit – CCU, CSRU (cardiac surgery recovery unit), MICU, and SICU (surgical ICU) – and non-liver lab tests such as serum creatinine, hemoglobin, and mean corpuscular volume (MCV). We also collected information on B12 supplementation and other interventions (dialysis, total parenteral nutrition (TPN), and inotropic support). Finally, we considered multiple disease conditions for inclusion in the final model: alcoholism, sepsis, respiratory disease, myeloproliferative disease, stroke, coronary artery disease (CAD), hypertension, other cardiovascular disease conditions not captured by any other comorbidities (Other CVD), immunocompromised status, gastrointestinal (GI) hemorrhage, and neuropsychiatric disorders. These potentially confounding variables were considered as candidates in the final model for a variety of reasons, either because they affect or are related to B12 levels (myeloproliferative disease, B12 supplementation, TPN, creatinine, hemoglobin, MCV), are known to affect liver function (alcoholism), or identify common subpopulations in the ICU (first service unit, CAD, stroke, hypertension, other CVD conditions not already captured by other information). We also considered for inclusion variables associated with chronic conditions that are known to be associated with higher mortality in the ICU, namely, dialysis, immunocompromised status, and respiratory disease. These chronic conditions are used in the APACHE-II (acute physiology and chronic health evaluation) score[25] which is an alternative to the SAPS score for measuring acuity in the ICU but, unlike the SAPS score, includes variables for pre-existing conditions. Most comorbidities were captured using ICD-9 codes, except immunocompromised status and alcoholism, which were supplemented with a manual review of the notes. Finally, we also collected variables included in the study by Sviri et al.[19] (inotropic support, sepsis, GI hemorrhage, neuropsychiatric disorders).