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Increased Vitamin B12 levels are associated with mortality in critically ill medical patients

S. Sviri[a,*], R. Khalaila[a], S. Daher[b], A. Bayya[a], D.M. Linton[a], I. Stav[a], P.V. van Heerden[a]

[a] Medical Intensive Care Unit, Hadassah-Hebrew University Medical Center, Ein Karem, Jerusalem 91120, Israel
[b] Department of Medicine A, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

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SUMMARY

Background & aims: We describe an observational study in critically ill medical patients showing the association between serum Vitamin B12 levels measured on or near admission and the outcome in these patients.
Methods: We used the database of patients admitted to the Medical Intensive Care Unit (MICU) at the Hadassah-Hebrew University Medical Center in Jerusalem, Israel, to analyze associations between patient demographics, background, diagnoses and serum Vitamin B12 levels with hospital and 90 day outcomes.
Results: Higher mean Vitamin B12 levels were found in patients who did not survive their hospital stay (1719 pg/ml vs 1003 pg/ml, $p < 0.01$). Those who had died by 90 days after admission to the MICU also had higher Vitamin B12 levels than survivors (1593 pg/ml vs 990 pg/ml). Regression analysis showed that elevated Vitamin B12 levels were associated with increased 90 day mortality, even after controlling for other variables. Survival analysis also showed an increased mortality rate in patients with Vitamin B12 levels over 900 pg/ml ($p < 0.0002$).
Conclusions: Our data show that high serum Vitamin B12 levels are associated with increased mortality in critically ill medical patients. We suggest that Vitamin B12 levels should be included in the work-up of all medical intensive care patients, particularly those with a chronic health history and increased severity of illness.

1. Introduction

Vitamin B12 is a water-soluble vitamin that is involved in lipid, carbohydrate and protein metabolism.[1] This vitamin is required for wellbeing throughout life and is particularly important for normal growth, bone marrow function and normal development and function of the nervous system. Vitamin B12 deficiency, its causes, the clinical entities resulting from it and its treatment have been described extensively.[2,3] Vitamin B12 and other vitamins have been trialed therapeutically in an attempt to reduce cardiovascular and other morbidity, unfortunately with limited success.[4–8]

More recently, the negative associations of high serum levels of Vitamin B12 are being recognized.[9–13] High serum levels of this vitamin are seen in the following conditions: renal failure, cancer, hematological malignancy (e.g. acute and chronic leukemias), polycythemia rubra vera, hypereosinophilic syndrome and hepatic disease (e.g. cirrhosis, hepatitis, hepatocellular carcinoma and metastatic liver tumors).[10,11,14] Increased Vitamin B12 levels are a result of one or more of the following mechanisms: Elevated plasma levels of transcobalamin I/III (a carrier protein, called also Haptocorrin, not involved in tissue uptake) produced by myeloid, hepatic and other cell types, increased hepatic cytolysis, decreased Vitamin B12 clearance by the liver, decreased production of transcobalamin II by the liver and hence decreased uptake by peripheral tissues or increased ingestion or therapeutic administration.[10,11,15] Circulating cobalamin binding protein and antibodies causing elevated plasma cobalamin levels were also reported.[16,17] Whether there is a distinct pathogenetic mechanism underlying the increased mortality among patients with elevated Vitamin B12 levels remains to be elucidated.

Although traditionally not considered an acute phase reactant, a weak association has been shown between serum Vitamin B12 levels and markers of sepsis (C-reactive protein levels) and the Sequential Organ Failure Assessment (SOFA) score in critically ill patients.[11,18] To our knowledge the serum Vitamin B12 level, measured during intensive care admission, has not been

* Corresponding author. Tel.: +972 2 6777111; fax: +972 2 6777920.
E-mail addresses: sigals@hadassah.org.il (S. Sviri), rabeik@hotmail.com (R. Khalaila), soldaher@gmail.com (S. Daher), bayya@hadassah.org.il (A. Bayya), dlinton@hadassah.org.il (D.M. Linton), ilanastav@hadassah.org.il (I. Stav), Peter.Vanheerden@health.wa.gov.au (P.V. van Heerden).

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investigated as an independent risk factor or marker for outcome in critically ill patients.

We undertook an observational study in critically ill patients presenting to our medical intensive care unit (MICU) over a period of seven years to determine the possibility of a correlation between serum Vitamin B12 levels and outcome.

2. Materials & methods

We have an extensive database for all MICU admissions at the Hadassah-Hebrew University Medical Center in Jerusalem, Israel, collected prospectively over a 7 year period (1.4.2003 – 30.6.2010). The dataset includes data on 2239 patients. Of these, 663 patients had their serum Vitamin B12 levels measured during their hospital admission. Indications for Vitamin B12 measurements include patients who have anemia, thrombocytopenia or neurological symptoms. ICU and hospital mortality are readily available and information on deaths subsequent to hospital discharge were available to us through linkage to the Ministry of Interior records.

2.1. Serum Vitamin B12 analysis

Serum Vitamin B12 analysis was performed in the Biochemistry laboratory of the Hadassah-Hebrew University Medical Center using the Siemens Immulite® 2500 Analyzer (PIL5KVB-11) using chemiluminescent enzyme immunoassay. Blood samples were obtained in heparinized tubes, and subsequent treatment of the specimens was performed according to the Operator's Manual. Normal values using this kit in our laboratory are determined as 200–900 pg/ml. Levels above 1200 pg/ml are subsequently diluted for accuracy. Serum Vitamin B12 levels were obtained from the computerized laboratory system. The levels chosen for investigation were those taken nearest to the ICU admission (mean 2.67 days following ICU admission).

Early feeding is standard in the MICU, preferably by the enteral route. The Vitamin B12 dose delivered by the most common enteral feeds used ranges between 6.3 and 12.6 mcg/L. In the very few patients who require parenteral feeding (14/663) the usual Vitamin B12 dose delivered is approximately 3 mcg/L.

Analysis of the data included the following steps, as further detailed below:

- Descriptive statistics and bivariate analysis of background and clinical variables in patients with available Vitamin B12 levels ($n = 663$), the B12 data set, and hospital and 90 day outcomes. Severity of illness analysis was used using the APACHE II score calculated 24 h after admission to the MICU.
- Multiple logistic regressions to determine outcome predictors for hospital and 90 day mortality.
- Long-term survival analysis comparing patients with a serum Vitamin B12 level less than or equal to 900 pg/ml, the "low B12" group and those with a Vitamin B12 level greater than 900 pg/ml, the "high B12" group. This discrimination level was used as 900 pg/ml is the upper limit of normal for serum B12 levels in our laboratory. A lower cutoff level of 400 pg/ml was initially considered and evaluated but resulted in a higher overlap of severity and outcome and attenuated the discrimination between patient groups compared to using an accepted pathological value of 900 pg/ml.

Waiver for informed consent for data collection performed in the MICU was approved by the institutional review board.

2.2. Data analyses

Descriptive statistics and bivariate analyses were used to calculate the mean and standard deviation of the continuous variables and the percentage and frequency of the categorical variables. Independent *t*-test and Pearson chi square tests were used to explore the relationship between the independent variables and binary outcomes (0 = alive, 1 = dead) at two points in time: hospital outcome, and 90 day (after ICU admission) outcome. Pearson Correlation was used to analyze correlations between Vitamin B12 levels and APACHE II score.

Next, we carried out binary logistic regression analyses for each outcome. In each regression, we analyzed the extent to which the B12 level predicts outcome, after controlling for the effects of background variables, chronic diseases, diagnoses, complications and Vitamin B12 measurements. Serum B12 levels were not normally distributed (positively skewed). We therefore used a log transformation for the logistic regression analyses.

Independent variables that had a significant association with the outcome variables were entered in each logistic regression analysis. Odds ratios and 95% confidence intervals were used to determine the effect of each predictor and whether it met statistical significance. Chi square tests and −2 log likelihood were used to determine whether the set of factors in each model reliably predicted the outcome. Nagelkerke's statistic (pseudo R2) was used to show the total variance accounted for in the models.

In addition, long-term survival analysis was performed using Kaplan Meier curves. As previously explained, a cutoff serum Vitamin B12 level of 900 pg/ml was used to define patient groups. Vitamin B12 level less than or equal to 900 pg/ml, the "low B12" group and those with a Vitamin B12 level greater than 900 pg/ml, the "high B12" group. Patients' survival was censored at the last mortality update (1.4.2010). Log Ranks analysis was used for significance analysis.

All data were collected prospectively and coded by a single operator to improve consistency. The Statistical Package for Social Sciences (SPSS) version 17.0 was used for data analysis.

3. Results

Table 1 shows the descriptive characteristics of the B12 sample group ($n = 663$) including variables such as chronic diseases, diagnostic categories at admission, APACHE II score, ICU and hospital mortality and length of stay. Nearly all of the patients had 2 or more criteria of systemic inflammatory response syndrome (SIRS). In a subgroup of 347 patients for which relevant diagnostic data were available, 325 (94%) had a diagnosis of SIRS. A positive correlation was found between Vitamin B12 levels and APACHE II score (Pearson Correlation 0.116 ($p = 0.003$).

Table 2 shows the descriptive statistics and bivariate comparisons of background variables and chronic diseases in the Vitamin B12 group ($n = 663$) for each outcome variable (hospital and 90 day mortality). It is evident that there is some association between background variables and chronic diseases and outcome. For example, age was associated with a higher mortality in each outcome period. In addition, the mean APACHE II score[19] was higher in those who died in each outcome period. Male gender was associated with a higher mortality at 90 days. Chronic diseases including immuno-suppression, chronic liver failure, and chronic renal failure were associated with increased mortality at each outcome period. In contrast, patients with chronic neurological diseases had decreased mortality compared to other disease groups, at both outcome periods.

Table 3 demonstrates the descriptive statistics and bivariate comparisons between diagnostic categories at admission and both