FINAL PROJECT REPORT – for PRO15/06

Date: 18/12/17

Name:

Anitra Carr

Project Title:

Vitamin C requirements in severe infection

Please copy the "Specific Objective(s)" statement, entered on your application form, in the space below.

Aim. The aim of this project was to determine the vitamin C status and potential requirements in severe infection (pneumonia and sepsis) and to assess potential anti-inflammatory activity by correlating levels with established biomarkers of inflammation.

Redefined Objective 1. To carry out a prospective study to analyse the vitamin C status of patients with community acquired pneumonia admitted to Christchurch Hospital.

Objective 2a. To measure vitamin C status and kinetics in patients with severe sepsis. 20 patients with severe sepsis will be compared with 20 matched ICU patients without sepsis.
Objective 2b. To correlate vitamin C levels in these patients with established biomarkers of inflammation (C-reactive protein, interleukin-6, procalcitonin).

Briefly describe how successful you were in achieving the stated objective(s). If the objective(s) was not achieved, explain why that is the case and describe what you did manage to achieve.

Objective 1

Our initial objective was to measure the vitamin C status of stored pneumonia patient plasma samples collected as part of the VIDCAPS study. However, little to no vitamin C was detected in these samples, which we believe was due to the blood samples being handled incorrectly for vitamin C analysis. Therefore, we redefined our objective to comprise a prospective study of vitamin C levels in patients with community acquired pneumonia. We have obtained ethical approval to prospectively measure vitamin C levels in up to 100 patients with community acquired pneumonia (HDEC 16/STH/235) on admission to Christchurch Hospital and 5 days later (or at discharge if earlier). This study is being carried out in collaboration with Prof Steve Chambers, an experienced infectious disease clinician.

To date, we have screened 71 patients, collected and analysed samples from 19 patients (including 5 follow up samples). Of the 19 patients, almost 90% had inadequate vitamin C levels (<50 µmol/L), nearly 50% had hypovitaminosis C (<23 µmol/L), and over 20% deficiency (<11 µmol/L); this is 10-fold more deficiency than we have observed in community-dwelling cohorts. We will continue to recruit up to another 20 patients in 2018 with the plan to publish the data. This status study will also provide pilot data to inform a randomized controlled trial of vitamin C administration in community acquired pneumonia.

Objective 2

Forty-four critically ill patients were recruited for this study. Twenty-four patients were categorized as having sepsis, seventeen patients were categorized into a non-septic cohort, and three were uncategorized. Plasma vitamin and C–reactive protein concentrations were measured daily over 4 days. Mean plasma vitamin C concentrations were significantly lower in septic patients (14.6 µmol/L, SD = 6.6) compared to the non-septic patients (19.7 µmol/L, SD = 9.3). Nearly 90% of septic patients were in the hypovitaminosis C category (i.e. <23 µmol/L) compared with 50% of the non-septic patients, and nearly 40% of the septic patients were deficient (i.e. <11 µmol/L) compared with 25% of the non-septic patients. These low plasma vitamin C levels were apparent despite receiving recommended intakes via enteral and/or parenteral nutrition (i.e. mean ~100-200 mg/d). Patients with sepsis had C-reactive protein levels 1.3-1.4 fold higher than non-septic patients, and significantly higher levels for the first 24 hours of the study compared to non-septic patients. Critically ill patients with hypovitaminosis C had significantly higher C-reactive protein levels, compared to patients with plasma vitamin C levels >23 µmol/L. In conclusion, critically ill patients have higher requirements for vitamin C than is being met by standard ICU nutrition practices. Septic patients, in particular, have significantly depleted vitamin C levels compared to non-septic patients, likely due to the elevated levels of inflammation associated with sepsis. This study has just been published (see details below).

Publication

Carr, A.C., Rosengrave, P.C., Bayer, S., Chambers, S., Mehrtens, J., Shaw, G. Hypo-vitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. Crit Care, 2017, 21:300. doi: DOI 10.1186/s13054-017-1891-y. Journal impact factor 5.4; journal ranking 6/86 (Q1), 1/15 open access (Critical Care and Intensive Care Medicine).

Outreach

I have presented this study at a number of conferences and public forums:

2017 (Sep). Invited oral presentation. 'Vitamin C requirements and mechanisms of action in sepsis', Symposium on Vitamin C, 9th Diet and Optimum Health conference, Oregon State University, Corvallis, USA (Symposium Co-organiser, Session Chair).
2017 (Jul). Oral presentation. 'Can vitamin C aid immune function in sepsis?' NZ Branch of the Australasian Society for Immunology (NZASI) meeting, Christchurch, NZ.
2017 (Jun). Invited oral presentation. 'Saving lives with intravenous vitamin C'. International Vitamin C Congress, Bad Homburg, Germany.
2017 (May). Invited public presentation. 'Vitamin C: snake oil or a valid therapy for infection?' Health Lecture Series, University of Otago, Christchurch, NZ.
2017 (Apr). Invited oral presentation – keynote speaker. 'Can we save lives with more vitamin C?' Australian and NZ Intensive Care Society (ANZICS) NZ Regional Meeting, Wellington, NZ.
2017 (Mar). Oral presentation. 'Vitamin C and inflammatory biomarkers in critically ill patients', Australian and NZ Intensive Care Society Clinical Trials Group (ANZICS-CTG) meeting, Noosa, Qld, Australia.

2017 (Feb). Invited oral presentation. 'Vitamin C for the prevention and treatment of disease', Kate Sheppard U3A group, Christchurch, NZ
2016 (Dec). Invited oral presentation, 'Vitamin C for the prevention and treatment of disease', Geraldine U3A group, Geraldine, NZ
2016 (Sep). Invited clinical presentation, 'Vitamin C requirement and mechanisms of action in severe infection', Division of Pulmonary Disease and Critical Care Medicine, Virginia Commonwealth University, USA.
2016 (May). Invited clinical presentation, 'Vitamin C requirement and mechanisms of action in severe infection', Infectious Diseases Department, Christchurch Hospital, NZ.

Briefly describe any interesting outcomes which might not have been considered in your original objectives (if any).

From the vitamin C stability issues encountered in the original objective 1, we have subsequently been able to clarify the optimal conditions for the handling and processing of blood samples for vitamin C analysis. This information will be used to inform vitamin C researchers and clinicians of the appropriate sample handling and processing conditions for vitamin C analysis of clinical samples. A publication of these findings has been prepared for submission to the Antioxidants special edition on "Vitamin C: current concepts in human physiology".

Additional biomarkers are being measured in the plasma samples from this study, e.g. the neutrophil enzyme myeloperoxidase (MPO), a marker of inflammation and infection. These biomarkers may be higher in critically ill patients with sepsis compared with patients without sepsis and, as such, could be clinically relevant biomarkers for sepsis. Although there have been ongoing issues with the ELISA assay used to measure MPO, preliminary evidence suggests that of the critically ill patients we have measured to date (n = 23), patients with sepsis (n = 13) have higher MPO levels compared with patients without sepsis (n = 10). This work is ongoing as the current data from our in-house MPO ELISA will be compared with commercially-available MPO kits.