Reviewer’s report

Title: Vitamin D to prevent acute lung injury following oesophagectomy (VINDALOO) - a randomised placebo controlled trial.

Version: 1 Date: 10 March 2013

Reviewer: Able Lawrence

Reviewer’s report:

Major Compulsory revisions

a) Time point for assessment of the primary endpoint "extravascular lung water index" is not clearly mentioned. [Day 1 post operative day is a very long period relative to procedure and onset of pulmonary edema. Authors have shown data to say that ELWI is stable within a 2 hour period but not over 24 hrs. Single or multiple time points can be measured (multiple pre-defined end points are preferable but since trial has already started, it is not possible) and in case of single end point, protocol should specify the timing of assessment.

b) Permuted block size of 5 cannot be used for equal distribution into two groups. The block sizes have to be even to get equally distributed two groups. [It is possible that the actual block size is ten (since the drug/placebo comes in packs of ten). If that is the case, then the protocol should be revised to reflect the same.

c) The secondary end points duration of ventilation days and hospital stay mentioned in statistical analysis are not mentioned under outcome measures. These would be very relevant and meaningful outcome measures.

Minor Essential Revisions

Discretionary revisions

The manuscript says “The only study looking at vitamin D levels in patients with severe sepsis suggests that these patients have a lower serum vitamin D level than ITU control patients” The study (Ref 26 Jeng et al) shows no difference between ICU sepsis and ICU control patients. Both groups had lower than healthy controls.

The manuscript says “This was associated with lower plasma levels of LL-37, suggesting that this deficiency is of functional importance in vivo [26]” The \( R^2 \) was 0.21 (\( P=0.05 \)) correlation was modest. Although this can be because of across the board low Vitamin D levels. It would be useful to include cathelicidin (LL-37) levels as well as serum/plasma cytokine levels. Cytokine bead arrays can estimate multiple cytokines in a single assays. Vitamin D response elements are known in the promoter regions of pro inflammatory cytokines.

Bioavailability of Intramuscular vitamin D is poorer (delayed rise in serum vitamin D) compared to oral vitamin D. However since study subjects have esophageal disease, route of administration is justified.
The study design is adequate to test the hypothesis regarding the efficacy of vitamin D in reducing post operative lung injury after oesophagectomy. However, the study misses opportunities to test covariates (potential biomarkers) that might explain the effects of any clinical response. While vitamin D is known to have pleiotropic effects on innate and adaptive immunity, the hypothesis regarding the role of cathelicidin is far from being proven in this setting. Additional studies done in the setting can improve the relevance of the study considerably by providing mechanistic insights.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I have no conflict of interest.