Reviewer’s report

**Title:** Vitamin C as an adjuvant for treating major depressive disorder and suicidal behavior, a randomized placebo controlled clinical trial

**Version:** 2  **Date:** 24 October 2014

**Reviewer:** Manuella P Kaster

**Reviewer’s report:**

This is a clinical trial evaluating the potential role of ascorbic acid as an adjuvant treatment for major depression in young adults. The study contributes to the field by adding clinical evidence to the growing body of pre-clinical research pointing to the relationship between ascorbic acid supplementation and antidepressant effects. However, the manuscript could benefit from improvement in a number of areas and an extensive English correction needs to be performed.

**Abstract:** The abstract needs a more detailed description

Point 1: Change major depressive disorder for MDD.

Point 2: Please correct the sentence: “One group recived citalopram plus vitamin C and the other group recived citalopram plus placebo.”

Point 3: The authors should change “Used to measure depression symptoms” for “Used to measure depressive symptoms”.

Point 4: The sentence “The adverse effects were checked too” should be changed for “We also evaluated the presence of adverse effects.”

Point 5: The conclusion needs to be more direct and clear. For instance… the supplementation with ascorbic acid did not increase the efficacy of citalopram in MDD patients.

Point 6: I didn’t understand the last sentence… No safety signal for this combination was identified during this trial.

**Background:** The background for the study should be elaborated. The authors should organize the introduction better, first talking about the involvement of oxidative stress in the neurobiology of depression, the antioxidant properties of antidepressants and than about ascorbic acid. After that, pre-clinical and clinical evidence about ascorbic acid and MDD should be presented.

Point 1: The sentence: “Some studies reported a positive correlation between inflammatory cytokines and suicidal behavior [20]” should be removed. Evaluation of inflammatory parameters is not the purpose of the study.

Point 2. The methods section could benefit from more structure and elaboration, specially the patient selection and randomization.
Point 3: Why did the authors choose to start with 10 mg/day of Vitamin C and increase the dose during the trial? In the discussion section the authors mention as a limitation the use of a fixed dose of vitamin C. This issue should be clarified.

Point 4: The authors should standardize week 2, week 4 and week 8 throughout the manuscript.

Point 5: Information about disease duration, number of episodes or age of onset would greatly contribute to the discussion. Is it possible that after several depression episodes the deterioration patterns caused by oxidative damage in the brain are no longer sensible to the administration of antioxidant therapy.

Point 6: Hamilton Depression Rating scale should be changed to HDRS

Discussion:
Point 1: “The results of this randomized double blind placebo controlled clinical trial indicate that the administration of vitamin C as an adjuvant medication with citalopram is not effective for treating depression symptoms in patients with major depressive disorder.” This sentence is incorrect, in fact the results show that the administration of vitamin C did not increase the efficacy of citalopram.

Point 2: Again, the information about anti-inflammatory agents such as celecoxibe and the decrease in inflammatory markers and depression symptoms seems lost.

Point 3: In my point of view, the lack of information about disease duration and number of episodes is the major weakness of the study. The antidepressant effect of Vitamin C in pediatric depression might suggest that this approach might be dependent on the illness duration. The authors should discuss that issue.

Level of interest: An article of importance in its field

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare no conflict of interest.