Author’s response to reviews

Title: Plasma glutamine levels in patients after non-elective or elective ICU admission

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Author’s response to reviews: see over
Dear editor,

Please find enclosed the revised version of our article entitled ‘Plasma glutamine levels in patients after non-elective or elective ICU admission; an observational study’.

Reviewer 1;
No further questions.

Reviewer 2;
We studied the publication of the REDOX trial by Heyland extensively. In this trial a total of 1223 patients were included, and in 61 patients (33 en 28) glutamine was measured prior to the start of supplementation. The measurements of the plasma glutamine level was performed afterwards and the value of the plasma glutamine level was not considered in the decision to start supplementation or not. So, there was some knowledge about the plasma glutamine level in a small part of included patients but these values were not part of the study protocol and were not considered in the decision to start glutamine supplementation or not.
I have changed the sentence in: “But in both studies supplementation was given without consideration of the plasma glutamine levels”. (Line 224)

This manuscript has not been published and is not under consideration for publication elsewhere. We do not have conflicts of interest of commercial affiliations to disclose. All authors have made a substantial contribution to the design of the study, acquisition of data and drafting / revising the article. All authors have seen and approved the final manuscript.

Yours truly,

Hanneke Buter
Reviewer: Kamal Medlej

Reviewer's report:

Discretionary Revisions
None

Minor Essential Revisions
1) Line 57: did you mean 6AM?

Reply:
Yes

2) Line 91: please describe why we should expect a difference in glutamine levels between elective and non-elective ICU admissions.

Reply:
This is indeed an important question. Previous studies have focussed on glutamine status mainly in patients with acute critical illness and sepsis. We questioned whether a low plasma glutamine level is caused by sepsis or inflammation. Our setting gave us the opportunity to focus on inflammation, caused by major surgery.
I have changed the sentence (Line 97-99);
Whether the inflammation that is caused by major elective surgery also leads to a decrease in plasma glutamine levels, comparable to the decrease during other forms of acute critical illness and sepsis is unclear.

3) Line 96: “In addition to this we aimed to compare the course over time in glutamine levels between the two groups during ICU stay “ unclear if this is part of the primary objective or a secondary objective

Reply:
This is a secondary objective, I changed the text accordingly ( line 101)

4) Line 117: did you mean 6AM?

Reply:
Yes

5) Line 153: you are comparing patient with elective surgery to patients with acute surgery and medical patients. Please make sure you elaborate on why you believe these 2 groups should be compared

Reply:
We compared the effect of inflammation on plasma glutamine levels in patients after elective surgery with patients who are admitted acutely with other forms of critical illness. That is the reason why acute admissions of medical patients and acute surgery are put in one group.
To give more clarity about the non-elective group I added this in line 113 in the method section.

6) Line 178: Please discuss why you believe there was a difference in the 2 Groups

Reply: the following sentences were added in the discussion.
Apparently, the inflammation caused by elective surgery can lead to a decrease in glutamine levels but is less pronounced compared to other forms of acute critical illness. The fact that patients who are admitted after elective surgery are very unlikely to have an infection at the time of admission on the ICU could also play a role in the difference between the two groups. Also, the time between the onset of an critical illness and admission to an ICU is generally longer than the time between start of surgery and admission, so it is conceivable that a longer period of catabolic stress leads to a further decrease in glutamine level. (line 183-190)
7) Please add to the discussion any perceived advantage (if any) of the glutamine level over the APACHE IV score.

Reply: added to the discussion (line 210 – 213)

If one considers glutamine levels solely as an additional risk factor, of course there is no additional advantage for glutamine over the well calibrated APACHE IV model. However, if one tries to unravel the ethology of organ dysfunction in pro-inflammatory disease states, our finding adds to the understanding that glutamine level may play a role.

Major Compulsory Revisions
8) Line 55: please mention the primary and secondary objectives

Reply: the following sentence was added to the method paragraph of the introduction.

The primary objective was to determine a difference in plasma glutamine levels upon non-elective or elective ICU admission. The secondary objective was to compare the course over time in glutamine levels and to determine the correlation between glutamine levels and severity of illness and presence of infection.

9) Line 209: Please rephrase the following sentence :"Reflects the presence of a low plasma glutamine level a deficiency or is it an adaptive stress response.

Reply: I rephrased the sentence.

Whether a low glutamine level during critical illness reflects an adequate response to stress or reveals a deficiency is not clear.(line 222)

Level of interest: An article whose findings are important to those with closely related research interests
Reviewer’s report

Reviewer: Daniel Dante Yeh

Reviewer’s report:
In this manuscript, Buter et al describe the results of a single center, observational study where they measured plasma glutamine levels in ICU patients at admission and for several subsequent days. They divided the patients into two groups (elective surgery and non-elective) and report that plasma glutamine levels were significantly higher in the elective surgery patients. They next performed a backward linear regression and report that glutamine levels were independently associated with severity of illness (APACHE IV) and presence of infection, but not with the type of admission.

General Comments: Overall, I found the manuscript enjoyable to read. The authors adhere to most standards of scientific writing and there are few, if any, errors in spelling, grammar, or style.

- Major Compulsory Revisions

1. Title: I recommend modifying the title to reflect your findings and also the type of study design.
   
   Reply: According to your suggestion I added the type of study design. I personally like a short title and adding the findings makes the title, to my opinion, too long.

2. Introduction: please elaborate more about why it is important to know about plasma glutamine levels in patients who are admitted after elective surgery (third paragraph)
   
   Reply: Previous studies have focussed on glutamine status mainly in patients acute critical illness and sepsis. We questioned whether a low plasma glutamine level is caused by sepsis or inflammation. Our setting gave us the opportunity to focus on inflammation, caused by major surgery.
   
   I have changed the sentence (Line 97-99); Whether the inflammation that is caused by major elective surgery also leads to a decrease in plasma glutamine levels, comparable to the decrease during other forms of acute critical illness and sepsis is unclear.

3. The main issue with this study is the question of relevance. In light of the two recent large RCTs (ref 14 and 15) what does your study add to the existing literature and our overall scientific understanding of glutamine in critical illness?
   
   Before this manuscript is acceptable for publication, the authors need to do a better job convincing the reader of the scientific importance of their findings. As they correctly point out in their discussion, it is debatable whether low glutamine levels in the critically ill are pathologic or adaptive. The current evidence does not support routine glutamine supplementation, especially in the critically ill or in renal failure. Given the low mortality rate and short ICU/hospital stay of the elective ICU admission group, I highly doubt that anyone would routinely supplement glutamine or measure it as a prognostic indicator.
   
   Reply: With measuring glutamine levels we want to go back to the drawing table. What I mean by that is, that we don’t really know what causes a low glutamine level and what the clinical
significance is of a low glutamine level. We know that a low glutamine level is associated with a worse outcome but we do not understand why. One of the problems thus far was that glutamine was not easy to measure and certainly not available for clinical use. The method that we have developed and used in this study gives us the opportunity to obtain a plasma glutamine level short after blood sampling and make a clinical decision whether or not to start supplementation. With this method we can investigate in future studies whether it is useful to supplement glutamine to patients with a low plasma glutamine level. The two large RCT which have been published recently showed no beneficial effects on mortality of supplementation of glutamine. But in both studies supplementation was given without knowledge or consideration of the plasma glutamine levels. At this time there is not enough evidence to supplement glutamine to all ICU or surgical patients but we hope that we can investigate this in the near future and answer some of the above mentioned questions.

4. I am having a little trouble understanding the statistical findings and I would like to request that the authors make it a little clearer. They first state that the glutamine levels were statistically significantly higher in elective compared to non-elective patients. However, on their regression model, they state that type of admission is not predictive. Does this not mean that the type of admission was strongly confounded by severity of illness and presence of infection? Is it accurate, then, to state that the levels were significantly higher when it was actually reflecting a confounder?

Reply
We found an association between glutamine levels and admission type in a univariate analysis, this analysis was followed by a multivariate analysis in which APACHE IV score and presence of a infection remained significant predictors of plasma glutamine levels. It is conceivable that the differences between the groups as observed in our study represent a confounder by severity of illness of infection. Patients who underwent elective surgery are less likely to have an infection.

- Minor Essential Revisions

1. Methods/Setting - first sentence: it is currently written as "every morning at 6.00 hrs pm" Do you mean "am"?
Reply:
Yes

2. Methods/Setting - second to last sentence: Please also specify how you handled BMI > 30.
Reply:
For patients with a BMI greater than 30, we used the weight patients would have had with a BMI of 30 [9]. (line 131)

3. Results: please maintain consistency in your terms. In the first paragraph of the Results section, you state, "The acute patients stayed longer...." By "acute" are you referring to the "non-elective" group?
Reply:
Acute is replaced for non-elective

4. Results: what is the significance of the 0.420 mmol/l cutoff? How did you choose this cutoff? Is it based on prior literature? If so, this should be referenced.
Reply:
It is an arbitrary cut-off point which is used throughout the literature. I added an extra reference in which this cut-off point is explained in more detail. [reference 6 Wilmore DW, Shabert JK. Role of glutamine in immunologic responses. Nutrition 1998;14:618-626.]

5. Figures: the figures do not add meaningfully to the results or the manuscript and I recommend deletion.
Reply: I understand your point. The figures are meant to give information about the reliability of the method we used for the plasma glutamine measurements. I would like to leave the decision whether the figures should be published to the editor.

6. Table: please also include BMI in your descriptive statistics
Reply: I added the BMI in table 1

Level of interest: An article of importance in its field