Author's response to reviews

Title: Glucose control in intensive care: Usability, efficacy and safety of Space Glucose Control in two medical European intensive care units

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Author's response to reviews: see over
Point by Point Response to Reviewers

Glucose control in intensive care: Usability, efficacy and safety of Space GlucoseControl in two medical European intensive care units

We would like to thank Professor Krinsley and Professor Van Herpe for their open review and their time resulting in very helpful comments that significantly improved our manuscript.

We have highlighted all changes in yellow in the revised version.

Reviewer Tom Van Herpe

Date: 20 March 2014

Amrein and colleagues tested the performance of the SGC system in two tertiary intensive care units. Overall, the manuscript stresses well the background of glucose control and how computerized algorithms may improve glucose control and patient safety. Further, the importance of efficient personnel training before implementing a new medical device has been justified. Some critical issues need to be addressed and clarified, however.

Major Compulsory Revisions

1. Due to the multi-centre approach of the study presented in the current manuscript two different studies (Graz and Zurich) seem to be combined. Authors mention that "selected data of the trial in Graz have been published previously". It is not clear what the difference is between the Graz data described in current manuscript and the Graz data published earlier [Efficacy and safety of glucose control with Space GlucoseControl in the medical intensive care unit -- an open clinical investigation. Amrein K, Ellmerer M, Hovorka R, Kachel N, Fries H, von Lewinski D, Smolle K, Pieber TR, Plank J. Diabetes Technol Ther. 2012...
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European intensive care units

Aug;14(8):690-5]. In both reports the data of the same 20 medical critically ill patients seem to be
described returning the same results. If this is the case, authors should focus on the unpublished data
(Zurich) in the current manuscript instead of mixing up two different data sets and averaging the results.

We appreciate these important comments. It is true that most of the Graz data have been published in
2012 and agree that is probably preferable to focus on the Zurich data as the setting was different (time to
inclusion, ICU staff handling and feedback). We have therefore amended Tables 1 and 3 and the
appropriate sections of the manuscript. Additionally, we simplified Table 3 as overall data on sampling time
and average glucose levels are also given in Table 2.

2. The claim that the medical device under study is now tested "under real-life" conditions is misleading
since the device was handled by a "dedicated study nurse" in the Zurich centre during daytime. Please
reformulate. It is also not clear whether the patients included in the study were treated by the SGC
system simultaneously or consecutively (cfr. section Study Population)? How was the end-of-study reason
"end of iv insulin need" defined?

Thank you for this attentive comment. It true that this was not a real routine setting, so we removed this
wording from the introduction setting.

At each study site, up to four SGC systems were available throughout the study period. Graz recruited from
February to December 2010, Zurich from August 2010 to August 2011. This information has been added to
the section Study Population.

End of insulin need was left to the judgement of the physician in charge of routine care and usually was the
time point when the patient started eating again.

3. Table 1: Data of two centres should be described separately; or only focus on Zurich data (see first
point).

We have now removed the detailed Graz data as they have been described previously and focus on the
Zurich data in Table 1 and throughout the manuscript.

4. Table 2: - Time gap from ICU admission to study start is rather large (particularly for Zurich: avg. 6.7
days). Please explain this in the manuscript as the period with typically most unstable glucose dynamics is
not incorporated in the study time. Reader can be misled when interpreting day results (e.g. Table 3). Was
the blood glucose controlled using the standard protocol in the period before the study start? - Report incidence of hypoglycemia (<2.2 mmol/l, <3.3 mmol/l) at patient level and at sample level.

Thank you for this comment. It is true that there is a large delay in study start at the Swiss site that is due to national ethical regulations. We have now added the following statement to the Results section:

**Baseline characteristics of the Graz population have been reported previously [28] and are similar except for a higher rate of norepinephrine and parenteral nutrition in Graz. Because of substantial national differences in informed consent procedure for patients unable to give consent at the time of study inclusion, time from ICU admission to study inclusion was significantly different between the two sites (Graz 1.7±1.5, Zurich 6.7±5.9 days, P=0.001). Before study start, blood glucose was controlled using the standard protocol.**

Indeed, before study start, blood glucose was controlled using the standard protocol. This has now been clarified.

The suggested different measures of hypoglycemia incidence have been added.

5. **Adherence to the SGC advices should be discussed in more detail.**

Please add:- insulin dose: magnitude of deviations? reason of deviations? - sampling time: was the proposed sampling frequency followed? type of deviations?

ICU nurses were asked to document when and why they overruled the system, however information is not complete. The magnitude of deviations ranged from 0.1 to 18.0 IU insulin/hour and the major reasons for overruling were subjectively too small or large changes in the advised insulin dose (e.g. ICU nurses set a rate of 5 IU insulin/hour instead of proposed 15, or 0.0 IU instead of 0.6 IU, also see the examples below) and simply feeling uneasy with the proposed insulin rate.
The sampling time was followed meticulously. These informations have been added to the manuscript.

**Minor Essential Revisions**

1. **Consort diagram and description of protocol violations (if any?) are missing**

### Table

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Actual Date/Time</th>
<th>Insulin Infusion Advice [Us/h]</th>
<th>Actual Administered Dose Rate [Us/h]</th>
<th>Current BG level [mM]</th>
<th>Next BG level [mM]</th>
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<td>4.5</td>
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</tbody>
</table>

40 patients were assigned for eligibility and met inclusion criteria

None were excluded because of exclusion criteria (insulin allergy, presence of ketoacidosis, moribund patients likely to die within 24 hours)

Informed consent was available for all patients

40 patients enrolled

48 patients were analyzed
The CONSORT diagram (see above) was not included in the manuscript as all 40 screened patients were enrolled and analyzed. No major protocol violations occurred. These informations have now been added in the manuscript.

2. Include the definitions of hypoglycemia (e.g. "moderate") in the Methods section

This is indeed an omission - we now added a paragraph on Definition of hypoglycemia in the Methods section.

3. Sampling interval varied from 1.3 to 3.0 hours (so maximum interval is 3 hours), while the Safety section describes a severe hypoglycemic episode "at the proposed time (i.e. 4 hours after previous glucose measurement) the blood glucose ..." Does the mentioned sampling interval take into account measurements that were not proposed by the SGC system?

We appreciate these important comments and agree that it was not clearly described. 1.3 to 3.0 hours were mean sampling intervals per 24 hours, but the maximum individual sampling interval that is given by the eMPC is 4 hours. The given sampling interval refers to all values that were entered in the SGC system. We have rephrased as follows in the Results section:

*The daily number of glucose sampling varied from 8 to 19 times (12 ± 2) and the mean sampling interval per day varied from 1.3 to 3.0 hours (2.2 ± 0.4).*

4. What is the percentage of nurses who used the SGC system and who filled out the questionnaire?

In Graz, 31 of 46 (67%) and in Zurich, 18 of 64 (28%) nurses filled out the questionnaire. This information has been added to the Methods section.

5. Figure 1: Indicate difference between blue and green profiles

Thank you for pointing out this omission. Blue lines are Zurich data, green lines are Graz data. This information has now been added in the Figure legend.
Amrein and coinvestigators have performed an industry-sponsored evaluation of the Space GlucoseControl, a computerized bedside decision support system created to improve glycemic control in 2 European ICU’s. The device integrates information from enteral and parenteral infusions, as well as insulin infusion, to provide guidance about insulin dosing. The manuscript is generally very well written and the patient population studied, albeit small, was quite ill, with mean APACHE II score 24.8 and 25% hospital mortality. The question posed by the authors is well defined and the experimental methods are appropriate and well described.

Major compulsory revisions

Please consider adding as a potential limitation the use of the bedside glucometers as the BG measurement device. There is a significant literature describing analytic inaccuracies associated with their use in critically ill patients. Please consider discussing as a potential limitation of the investigation the BG measurement interval. The mean interval of 2.2 hours was likely associated with “missed” hypoglycemic and hyperglycemic excursions (described in other literature that used continuous or near-continuous measuring devices). In fact, the single episode of severe hypoglycemia that occurred in the cohort was an example of this; the previous BG measurement had been obtained 4 hours earlier. The investigators note that 15% (6/40) of the patients sustained moderate hypoglycemia (associated with increased risk of death in the literature); this reviewer suspects that a higher measurement frequency may have identified a higher percentage. There is confusion about description of the primary endpoint – whether it is percentage of values in the target range or time in target range. Please see Page 8 and Table 2, as examples. The subjective assessments of the 2 different nursing staffs are referred to in the text at the end of the Results section and explored in some detail in the Discussion section. Review of Table 4 reveals dramatic differences between the 2 units. The Zurich ICU nurses had a remarkably adverse opinion of the device, with concerns about workload, reliability, efficacy, etc, even though there was a study nurse who helped during daytime hours (Page 7). Since this device is commercially available (in Europe) and readers of this study may wish to consider use of the device in their own ICU, further discussion of this feedback from the bedside users seems warranted.
Thank you for the extensive and constructive review of our paper. We have added both important suggested limitations in the Discussion section:

“Another limitation is the use of bedside glucometers as they were originally developed for glucose measurement in another setting and are not accurate enough for glycemic control in critically ill patients, especially when anemia is present [33-34]. Moreover, the mean sampling interval of > 2 hours is a potential limitation as in comparison with continuous glucose monitoring, hypo- and hyperglycemic excursions of blood glucose may have been missed, as also described in the literature [35].”

We made a mistake in the description of the primary endpoint in the original submission, thank you for this attentive comment. The primary endpoint was the **time in target range**. This has now been clarified in the paper throughout.

**METHODS:** The percentage of time within the predefined glucose target range (4.4-8.3 mmol/l) was defined as primary endpoint for the assessment of glucose control.

**DISCUSSION:** As demonstrated in our two centers, it was possible to achieve excellent adherence and glycemic control at both sites, with low variability and the target range of 4.4 to 8.3 mmol/l could be achieved in 88 percent of the time.

We further considered potential causes of the diverse opinions of ICU staff at the two sites and now reformulated the Discussion section:

*In Zurich, glucose control was outstanding and significantly better than in Graz, yet the involved ICU staff turned out to be unsatisfied. We hypothesize that this difference was caused by 1) the intensive hands-on simulated training performed only in Graz and 2) the long lasting routine use of BBraun pumps at the same site. Although the training was a time-consuming and laborious process, it nevertheless seems to be necessary when implementing such a new tool in order to assure long-term functionality and operator satisfaction within the ICU team. The fact that infusion pumps from another manufacturer are in use in Zurich meant that ICU staff needed to become familiar with even more new equipment and had to handle two different types of pumps at the same time. This is particularly evident in the response to question 8 regarding potential routine use which was viewed favorably by 70% of nurses in Graz, but only 11% in Zurich.*
Minor compulsory revisions

I would recommend avoiding unnecessary adjectives. For example, Abstract/Conclusions: “…two large European medical intensive care units;” Page 4, Introduction: “…euphoric reactions;” Page 6, Methods “…two large tertiary academic centers.”

Page 4 – Please consider adding citations to the first sentence of the 2nd paragraph: (“Poor glycemic control represented by hyperglycemia, hypoglycemia and high variability is strongly and consistently associated with poor clinical outcomes.”)

Page 4 - Please consider revising the sentence that includes “…one of the least common denominators.” This phrase is unclear. The authors may wish to cite the large study done by Juneja et al, evaluating a computer-assisted insulin dosing algorithm in a very large cohort of critically ill patients (2,398) – Diab Tech Ther 2007 (93):232-240.

Page 4 – please change “…the quality of GC besides reducing workload” to “the quality of GC and reducing workload.”

Page 9 – please change “…more favorable” to “more favorably.”

Table 1 – Does the admission diagnosis “Resuscitation” mean post cardiac arrest?

Figure 2 seems to be a repeat of the data detailed in Table 4. In addition, the designations “Delios 01” and “Delios 04” are unclear. Perhaps the Figure should be removed.

Thank you for these additional comments.

- We have changed/revised the wording as suggested. It is also true that Figure 2 is a repetition of data already found in Table 4, it has therefore been removed.
- The references have been updated and extended including the suggested reference.