Author's response to reviews

**Title:** Implementation and evaluation of a nurse-centered computerized potassium regulation protocol in the intensive care unit: a before and after analysis.

**Authors:**

Miriam Hoekstra (m.hoekstra@thorax.umcg.nl)
Mathijs Vogelzang (m.vogelzang@thorax.umcg.nl)
Jose T Drost (j.t.drost@student.rug.nl)
Marcel Janse (m.janse@student.rug.nl)
Bert G Loef (b.g.loef@thorax.umcg.nl)
Iwan CC van der Horst (i.van.der.horst@thorax.umcg.nl)
Felix Zijlstra (f.zijlstra@thorax.umcg.nl)
Maarten WN Nijsten (m.w.n.nijsten@chir.umcg.nl)

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**Author's response to reviews:** see over
Dr Melissa Norton

Editor-in-chief

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Subject: Revised manuscript 7038556372816137

“Implementation and evaluation of a nurse-centered computerized potassium regulation protocol in the intensive care unit: a before and after analysis”

Miriam Hoekstra, Mathijs Vogelzang, José T Drost, Marcel Janse, Bert G Loef, Iwan CC van der Horst, Felix Zijlstra, Maarten WN Nijsten

Dear Dr Melissa Norton,

Hereby we send you the revised version of our manuscript “Implementation and evaluation of a nurse-centered computerized potassium regulation protocol in the intensive care unit: a before and after analysis” (MS 7038556372816137).

In the revised manuscript, all changes are highlighted. Below you find our point-by-point response to the reviewers.

The comment that the potassium source code was not available on the website cited was a misunderstanding. The online available source code of GRIP has the GRIP-II potassium algorithm incorporated. As requested, several additional baseline characteristics and potassium infusion data were added to the manuscript. We think we have adequately addressed all issues raised by the reviewers.

We hope that the manuscript in the current form is suitable for publication in *BMC Medical Informatics and Decision Making*.

Sincerely, on behalf of all co-authors,

Miriam Hoekstra, MD (corresponding author)

University Medical Center Groningen,
Department of Cardiology
PO 30.001
HANZEPLEIN 1, 9700 RB Groningen, the Netherlands

Revision Letter 11.11.09

MS 703855637281613
Email: m.hoekstra@thorax.umcg.nl
Tel: 0031-50-3611413
Fax: 0031-50-3611347
Point-by-point response

Reviewer: Shigehiko Uchino

Hoekstra et al. conducted a before-after study looking at the impact of implementing a computerized protocol for serum potassium level control in critically ill patients. They found that computerized potassium control was effective and reduced the prevalence of hypo-and hyperkalemia compared with previous physician-driven potassium regulation. This study is well conducted and the manuscript well written. However, this study contains some problems in generalizability, which needs to be discussed more thoroughly.

Major Compulsory Revisions

In their unit, the computerized protocol should be implemented without major difficulty because they had used a similar protocol for glucose. It is likely that most hospitals are not using such a computerized system and would not be easy for such hospitals to implement it.

Answer: This is a good point that we added to the discussion section. Indeed, our nurses were already used to the GRIP program and implementation in an ICU not used to work with a computerized decision support system would take more effort.

It is not clearly written how abnormal potassium level was dealt in the before period and how their ICU was run (open or closed ICU). For example, according to the method section in the manuscript, potassium intake was reviewed by the attending physician only daily, except for cases of markedly abnormal potassium levels. It is also not mentioned how often and when nurses called doctors for abnormal potassium levels. In my knowledge, most ICUs in the Netherlands are closed ICUs and are covered by intensivists for 24-7. If so, it would not be difficult for ICU physicians to review potassium intake more frequently and for nurses to consult physicians about potassium management.

Answer: The ICU format is closed, as now mentioned. The policy towards abnormal potassium levels was not explicitly formulated in a quantitative protocol, as is the case in many ICU’s for many laboratory values. Nurses additionally contacted the physician for 30% of the patients each day with questions regarding potassium regulation. We agree that it is not difficult for our nurses to contact physicians. That is however not a reason not to involve physicians in all minor derangements of a patient. The necessary (telephonic) consultations with the attending physician may be viewed as neither particularly efficient nor optimal as physicians caring for ICU patients have more than sufficient inherently complex patients to handle, many of which cannot be handled by algorithms such as GRIP. This description of the way potassium levels were handled before the implementation of GRIP-II is added to the revised manuscript.

Nowadays, due to the rare, but serious accidents of inadvertent potassium injection, many hospitals have abandoned using concentrated potassium. Continuous concentrated potassium infusions shown in this study cannot be implemented in such hospitals. Authors should mention for safety of using concentrated potassium and for generalizability of their findings in such hospitals.

Answer: Safety is a major topic, and indeed an injection of concentrated potassium can easily lead to (potentially fatal) complications. Therefore, in our institution on the general ward and for all potassium bolus injections we indeed use diluted potassium chloride. However, on the ICU the majority of patients receive continuous potassium suppletion by syringe pump. To
avoid dosing errors, we use a 1:1 (1mmol/1ml) solution in the syringe pump. So when a syringe pump is on 3 ml/hour the nurse/physician can easily see that the patient receives 3 mmol of potassium per hour. Moreover, especially in the ICU concentrated potassium infusions are often a necessity because of fluid restrictions.

When other ICUs use diluted potassium for continuous infusion, the advice that GRIP-II provides (e.g. potassium pump rate of 3 ml per hour) can be easily converted according to the used solution so that 3 mmol/h is administered to the patient. We added parts of this discussion to the manuscript.

Minor essential revisions
Page 9, 2nd paragraph: Figure 3, not figure 4.

Answer: We corrected this mistake.

Reviewer: Hiroshi Morimatsu

This is the study to assess the efficacy of the implementation of a computerized potassium regulation protocol in the ICU. They conducted before-after comparisons for their protocol implementation. They have already used a computerized glucose regulation protocol (GRIP) system. And they had added a potassium regulation protocol to GRIP. They evaluated potassium regulation with this protocol system. They studied 2210 patients totally and found that the incidences of hypo- and hyperkalemia were significantly decreased after the implementation of protocol, although the median values and their time-course of potassium were not different. They also found that the time spent in the abnormal range of potassium decreased after the implementation of the protocol. They concluded that the computerized potassium control is safe, effective and reduces the prevalence of hypo- and hyperkalemia in the ICU.

This is an interesting study and they showed that this system is useful to reduce the prevalence of abnormal values of potassium. The manuscript is well written and their findings reasonably discussed. However, I have some concerns and suggestions to the authors as shown below.

Major compulsory revisions.

To evaluate the incidence and prevalence of abnormal potassium levels, they only used actual rates. I think odd ratio would be more informative in this analysis. Please provide odds ratio for the incidence and prevalence of abnormal potassium levels.

Answer: Like you suggested we added the odd ratios (OR) and confidence intervals (CI) for the incidence and prevalence of abnormal potassium levels in our revised manuscript.

For potassium control, they only reported the results of potassium control. I think it is important to report the details of potassium administration. How many patients received potassium infusion? What is the average rate of infusion? How long were patients on potassium infusion? Etc. Please provide the information about potassium infusion.

Answer: Data about potassium infusion were added to the manuscript.

Most exciting results of this study is that this system improves potassium control without the increased risk of hyperkalemia, because this algorithm only have potassium infusion, but not potassium decreasing protocol. This point should be emphasized in the discussion.
**Answer: We have added this valid point to the discussion section.**

Minor essential revisions

Page 4, last part “physician driven” should be “physician-driven”

**Answer: We corrected this in the revised manuscript.**

Page 13, second paragraph, “physician driven” should be “physician-driven”

**Answer: We corrected this in the revised manuscript.**

Reviewer: Karl Werdan

1.0 BACKGROUND

1.1 Medication errors are not investigated in this study. Elaboration on this topic is misleading in the introduction.

**Answer: We changed this accordingly and removed the “medication” notion in the introduction.**

1.2 Whether or not the implementation of GRIP-II causes only “marginal additional costs and virtually no extra effort “was not assessed in this study. It can hence not be part of the “hypothesis”.

**Answer: We deleted the reference to costs to avoid the suggestion that we performed a formal cost analysis. However, we definitely assessed the impact on effort required on the part of the nurses and doctors.**

1.3 The exact aim of the study should be clearly stated either at the end of “Background” or in “Methods”. A sentence such as “… we describe the extension of a GRIP” is narrative and thus insufficient.

**Answer: We changed the last sentence of the background part accordingly. We also modified the hypothesis part in the introduction section.**

2.0 METHODS

2.1 It is referred to a “physician protocol” and “these guidelines” with regard to the situation before GRIP-II. The process of potassium regulation before GRIP-II needs a sound description.

**Answer: We now describe this process as accurately as possible.**

2.2 Why was consultation of an ethics committee not deemed necessary?

**Answer: We did consult the ethics committee and this study was approved by the institutional review board (i.e. the ethics committee). This is stated in the text.**

2.3 “In a recent study…”-discussion should be avoided in “methods”, the paragraph should be kept functional.

**Answer: We deleted this part of the methods section.**

2.4 “The GRIP-II potassium algorithm…” this is trivial and could be spared.
Answer: We are aware that this is a very simple algorithm. However it may be quite relevant to share such details with interested readers.

2.5. The methods need a statement that nothing else changed during the study period, otherwise all changed (e.g. changed glucose target range or insulin sliding scale for intensive glucose control) should be clearly listed.

Answer: We cannot truthfully claim that nothing changed, because things always change. However, in the field of relevance (potassium and glucose control) no conscious changes were made.

2.6. The exact study period dates should be stated.

Answer: We added the exact study period to the manuscript.

2.7 Fig 2 is to appear as a detailed chart that puts a programmer in the position to write a programme such as the GRIP-II. All hidden formulas such as “predicted potassium clearance” or “estimated creatinine clearance” should be explicit. How was the presence of renal replacement therapy incorporated in the algorithm?

Answer: To estimate (or “predict”) the creatinine clearance the Cockroft-Gault formula was used. We added the description of how the predicted potassium clearance is incorporated into the potassium infusion algorithm to the revised manuscript.

2.8 “…advised this rate...”- this is not in accordance with Fig.2 as it seems to depend on GFR, potassium and presence of hemofiltration.

Answer: You are correct, the advised infusion rate is also dependent of the estimated potassium clearance and the presence of hemofiltration.

2.9 “…i.e., potassium <2.8 or > 6.0 mmol/L...” – this is not in accordance with fig.2 as it depends on diuresis or GFR, respectively.

Answer: In case of a GFR<30 ml/min or diuresis <30 ml/hr the target range lowers to 3.6-4.3 mmol/h instead of 3.8-4.5 mmol/h. So indeed, in case of renal failure the thresholds to alarm the physician are not <2.8 mmol/L and >6.0 mmol/L but 2.6 mmol/L and 5.8 mmol/L. We corrected this mistake in the manuscript.

2.10 What is the rationale behind the proposed GRIP-II algorithm and its cut-offs?

Answer: The rationale behind the various constants that were put into the algorithm is strictly empiric. It was also based on published potassium values considered to be dangerous.

2.11 “The reference range of arterial potassium...” – no need for this statement.

Answer: We removed this statement.

2.12 “Patients received potassium either”- this is redundant as it is described twice in this paragraph.

Answer: We corrected this in the revised manuscript.

2.13 “Before implementation of GRIP-II...” this should be described above (see 2.1)

Answer: In the revised manuscript we describe this better now.
2.14 How was the decision reached regarding the administration route (parenteral vs enteral)? How were reflux/gastroparesis/diarrhoea managed? Was there an enteral night pause?

Answer: Potassium was given preferably enterally. No enteral night-pauses are applied in our institution.

2.15 Was the nurse questionnaire anonymous? At what time during the implementation did they complete the questionnaire?

Answer: The questionnaires were anonymous and they were filled out after the GRIP-II was part of routine care for six months. This information was added to the manuscript.

2.16 “Prevalence of hypokalemia...” the term “incidence” should be better considered instead?

Answer: We defined “incidence of hypokalemia” as the number of measurements in the hypokalemic range. The prevalence of hypokalemia was defined as the duration in the hypokalemic range divided by the total duration of ICU stay. We added this explanation of the definition of “incidence of hypokalemia” to this paragraph.

2.17 It is not clear how the “duration of hypokalemia or hyperkalemia” was calculated from the point measures obtained. (e.g., what is the duration if, between two values within range, just one value was hypo- or hyperkalemic?). En explanation is obligatory. Giving just the number of hyper-/hypokalaemic measurements would be more intuitive.

Answer: The percentage of measurements in the hyper-/hypokalemic range for both the before and after period are already mentioned in the manuscript (“incidence of hypo-/hyperkalemia” is defined as the number of measurements in the hypo-/hyperkalemic range). A disadvantage of this method is the variable sampling rate; when a patient is out-of-range GRIP-II advises more frequent measurements than when the patient is within the predefined range. We used a method that takes into account the unequal sampling distribution. All measurements and their time distribution were used to calculate each patient’s potassium curve using linear interpolation. The time within the hypo-/hyperkalemic range is divided by the total length of stay to calculate the prevalence of hypo-/hyperkalemia. The same method is used to calculate the hyperglycemic index (HGI) developed by Vogelzang et al [1]. An example of linear interpolation (and what happens when only one value is out of range) for glucose levels is adapted from this publication:


This reference, and part of our explanation are added to the revised manuscript.

2.18 “Skewed data” –How was skewness tested?
Answer: Skewness of data distribution was assessed by calculating kurtosis with SPSS.

2.19 What was the level of significance?

Answer: Differences were considered significant for a two-tailed P value <0.05 (information added to the manuscript).

2.20 Information on blinding/role of the data acquisition staff is advised.

Answer: As a logical consequence of the study design neither nurses nor physicians were blinded. Data was retrieved automatically from the hospital information system.

2.21 It is mandatory to clearly state primary and secondary endpoints of the study.

Answer: The primary and secondary endpoints of our study were added to the methods section.

3. RESULTS

3.2 “There were no baseline differences...” might be right according to the data presented. Whether or not applies to the groups studied is, based on the data presented, just a broad estimation. The following baseline data should be included in table 1 both to characterize the cohort studied (and thus to characterize the cohort to which the results apply) and to be surer about the conclusion “no baseline differences”.

-What was the illness severity of the patients? (e.g. APACHE-II-Score)

Answer: APACHE-II scores were added to the revised manuscript.

- What was the prevalence of chronic kidney disease, chronic dialysis, and the GFR at baseline?

Answer: Baseline creatinine was added to the revised manuscript.

- What was the incidence of acute kidney injury during the study?

Answer: The incidence of acute kidney injury was added to the revised manuscript.

- What was the rate of renal replacement therapy?

Answer: The rate of renal replacement therapy during ICU admission was added to the revised manuscript.

- What was the baseline potassium?

Answer: Median (IQR) baseline potassium was 4.0 (3.7-4.3) mmol/L before the introduction of GRIP-II and 4.0 (3.7-4.4) mmol/L afterwards (see also figure 3).

- How many patients received potassium enteral/parenteral?

Answer: We did not classify and record this separately since many patients received both modalities.

3.3 “Figure 4” is missing

Answer: It must be “Figure 3” instead of “Figure 4”. We corrected this mistake.
3.4 How does the diagramme relate to the primary and secondary endpoints? As a “time course of potassium” was not prespecified in the methods section, this appears arbitrary here.

**Answer:** As asked for, potassium regulation is now mentioned as a primary endpoint. Figure 3 displays potassium regulation.

3.5 “The median level or their time course…”- this is incomprehendable. Figures (i.e. numbers) are not given. How does this relate to the primary and secondary endpoints (still to be defined). If this is a relevant endpoint of the study it is to be described in the methods section and accompanied by a table with the respective figures.

**Answer:** Here also we refer to the primary endpoint, that is, the potassium regulation.

3.6 “After the first 8h of ICU admission”- How does this relate to the primary and secondary endpoints (still to be defined). If this is a relevant endpoint of the study the cutoff of 8hrs is to be explained in the methods section.

**Answer:** The endpoints are now mentioned in the methods section.

3.7 “(defined as…” this is methods not results.

**Answer:** This part was moved to the method section.

3.8 “of hypokalaemia” duplication of words.

**Answer:** We corrected this mistake.

3.9 “In 14 patients…” How does this relate to the primary and secondary endpoints (still to be defined). This statement follows no systematic plan.

**Answer:** It follows the primary endpoint as it demonstrated the ability of GRIP-II to rapidly correct potassium.

3.10 “…compared to the old paper protocol…”-which one?

**Answer:** This indeed is confusing and we now have removed this reference.

4. DISCUSSION

4.1 There is no relevant contribution of the 2nd paragraph of the discussion. Consider deletion.

**Answer:** This part expands on our findings and the specific new features of GRIP.

4.2 “…since such factors…”- unfortunately we were unable to understand the meaning of or the idea behind this sentence.

**Answer:** We agree so this sentence was rewritten.

4.3 “…did not add any significant nursing time or costs…” – we suggested a clear expression that this statement is not a conclusion of the study but a frank estimation of the scientists as time and costs have not been measured in this study.

**Answer:** We agree that costs are not formally measured. We now mention more precisely the work involved in terms of effort spent by the nurses and contacts concerning potassium control with physicians.
4.4 What was the reason for nurse`s noncompliance in the first few weeks of implementation and how could potential obstacles be overcome?

**Answer:** The nurses had to adapt to computer provided advices. This took time. The importance of education is now mentioned in the discussion.

4.5 In our view the comparison between a nurse paper protocol and GRIP-II was an even more relevant study subject. The authors should refrain from suggesting that the computer is better than an paper protocol just from extrapolating from earlier findings. The superiority of the computer algorithm over paper-protocols published elsewhere is not the result of the presented study.

**Answer:** We agree and we do not want to make such sweeping decisions on the basis of our data.

5.0 Limitations

5.1 How could a Hawthorne effect have interfered?

**Answer:** This is an interestingly question, but in its essence we compared previous “human” control with computer-driven control and computers should not be sensitive for the Hawthorne effect.

5.2 Does “… the sharpened glucose control during the study period” mean that other interventions have interfered with the study intervention? This needs definite explanation.

**Answer:** This is indeed one of the studies limitations, as we noted in the discussion.

5.3 It is suggested that limitations of the nurse survey be included.

**Answer:** The limitations are now noted.

6.0 Conclusions

6.1 Safety has not been evaluated in this study.

**Answer:** We did evaluate potassium derangements. Extreme derangements significantly decreased. In our view this improves safety.

7.0 Note

7.1 The GRIP-II source code is NOT available from the website cited. Instead, as document length is no issue in BMC, it is suggested to incorporate it to the paper as an attachment.

**Answer:** We are sorry for the misunderstanding, but the online available source code of GRIP has the potassium algorithm incorporated. We will make this clearer on the website.