PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

| TITLE (PROVISIONAL)          | An Observational Study of the Relative Efficacy of Insulin-glucose Treatment for Hyperkalaemia in Patients with Liver Cirrhosis |
|-------------------------------|---------------------------------------------------------------------------------------------------|
| AUTHORS                      | Lim, Andy; Crnobrnja, Ljiljana; Metlapalli, Manogna; Jiang, Cathy; Wang, Rene; Pham, Jeanette; Abasszade, Joshua H. |

VERSION 1 – REVIEW

| REVIEWER                      | Robert, Thomas |
|-------------------------------|----------------|
| Hôpital de la Conception      |                 |
| REVIEW RETURNED               | 10-May-2021     |

| GENERAL COMMENTS              | The authors report a decrease effectiveness of insulin-glucose treatment of hyperkalemia in patients with cirrhosis. |
|-------------------------------|---------------------------------------------------------------------------------------------------|
|                               | In the methods, the authors should detailed the procedure (duration, intravenous infusion systems used, material of bag or syringe (polyvinyl chloride or polyurethane, polypropylene) precisely in each center and verify that the material has not change during all the study to administrate the insulin-glucose therapy and cite this article (doi: 10.1093/ckj/sfab033). |
|                               | In the baseline characteristics, the authors should precise: AKI KDIGO Stage and proportion of hepatorenal syndrome, serum creatinine and urea at admission and diuresis, amonemia, cardiac manifestations of hyperkalaemia, ascites and hepatic encephalopathy in the cirrhotic group at admission, history of hyperkalaemia and Sodium polysterene sulfonate or other resin exchange use at admission. |
|                               | In the univariate analysis, the authors should include the center. It will be interesting that the authors show if the insulin-glucose treatment effectiveness is dependent of the cirrhosis severity according to Child-Pugh score. |
|                               | The authors should report the adverse events like hypoglycemia in the 6 hours after the treatment. |
|                               | Figure 2 is not clear. The author should clarify what represent change in potassium. |

| REVIEWER                      | Rafique, Zubaid |
|-------------------------------|----------------|
| Baylor College of Medicine    |                 |
| REVIEW RETURNED               | 21-May-2021     |

| GENERAL COMMENTS              | Thank you for inviting me to review this manuscript. This is certainly an interesting and important study. Overall the objectives are clear and the manuscript is well-written. Following are my concerns: |
|-------------------------------|---------------------------------------------------------------------------------------------------|
1. Fig1 - pt enrollment flow diagram shows that control and treatment groups were enrolled at different time periods. Treatment and practice patterns change over time. Is there a reason why the control group was not enrolled over the same time period (vs. only during Jan 2019-Mar 2020)? This introduces additional confounders and need to be addressed.

2. Table 2 lists co-treatments. Newer binders (Lokelma and Veltassa are missing from this list. Were they not available at this hospital or data not collected? Potential confounder if not accounted for.

3. Table 2: salbutomol use. Seems like the control group used twice as much as the cirrhosis group (12.7% vs. 6.3%; \( p=0.11 \)). Although not sig, this is a potential cause of the larger delta K in the control group. This together with the fact the that more cirrhotic pts were on beta blockers which may reduce the efficacy of albuterol could explain the smaller K change. This should be highlighted in the discussion section.

4. Total insulin and salbutamol doses should be compared between groups (and not just number of treatments). As we know that hyperkalemia treatment is not standardized and so same number of treatments does not mean same amount of drug.

5. If I understand correctly, the hypothesis is liver disease makes insulin less effective in reducing K. Is it possible to show that worsening liver disease causes increasing insulin resistance and thus poorer K change?

This is an important piece of work and should be published once the above limitations are addressed.

Thank you.

REVIEWER
Scott, Nathaniel
Hennepin County Medical Center

REVIEW RETURNED
25-May-2021

GENERAL COMMENTS
I thank the authors for their contribution. Interesting and well-written paper. The question is of clinical significance. Appropriate methods for a first investigation in to this topic. Use of univariate and multivariate regression supports the analysis.

Three items I would recommend addressing in a revision

1. The timing of the post-insulin potassium checks. There was some criteria discussed for what would be considered acceptable - 2 checks within 6 hours, at least 1 within 2 hours, I believe. This was a bit confusing and could be more clearly described. It seems that the lower of the values was used, but this should clarified. Because the potassium lowering effect is rapid and dynamic, the lack of standardized time at which the potassium was checked afterwards is a limitation and a potential confounder. Would recommend reporting the time at which the potassium was checked (relative to the administration) of insulin for the two groups and performing statistical analysis to see if it is different.

2. A limitation is that the patients in this study are identified by ICD-10 diagnosis of hyperkalemia. This requires that this diagnosis be coded, and there are likely other patients that had insulins and dextrose treatment of hyperkalemia in these hospitals during this time period that did not receive this code. This may have been the most practical way for the authors to identify this population. Would recommend addressing this limitation in the
paper and would ask the authors to speculate if this would result in any selection bias.

3. Lastly, hypoglycemia is a well-described complication of the use of insulin and dextrose for the treatment of hyperkalemia. The decision about whether to administer insulin/dextrose and the doses of each should involve a considering of the risks/benefits. If the data is available, would be important to report other clinically significant outcomes of this treatment, such as the proportion that experienced hypoglycemia in each group. One could hypothesize that this could be higher in the cirrhosis group.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1  
Dr. Thomas Robert, Hôpital de la Conception

Comments to the Author:

The authors report a decrease effectiveness of insulin-glucose treatment of hyperkalemia in patients with cirrhosis.

1. In the methods, the authors should detail the procedure (duration, intravenous infusion systems used, material of bag or syringe (polyvinyl chloride or polyurethane, polypropylene) precisely in each center and verify that the material has not change during all the study to administrate the insulin-glucose therapy and cite this article (doi: 10.1093/ckj/sfab033).

Reply: All study sites used a standard protocol for insulin-glucose treatment as part of an established healthcare network policy and procedure document endorsed by the Medication Safety and Therapeutics Committee and Chief Medical Officer. Medical supplies for all sites were also centrally managed across the network hospitals so there was no variation in materials used. Briefly, 10 units (0.1 mL) of short-acting insulin is drawn into an insulin syringe and added to a 50 mL glass vial of 50% glucose (0.2 units/mL) and mixed well by repeated inversion. The mixed contents are drawn into a standard 50 mL polypropylene syringe and immediately administered via a syringe driver over 15-30 minutes. The use of a standard protocol, polypropylene syringes and identical materials avoids significant variations in intravenous insulin delivery which may be observed when different materials or infusion times are used. We have included this information in a new subheading of “Insulin-glucose treatment” in the Methods section and cited the recommended article.

2. In the baseline characteristics, the authors should precise: AKI KDIGO Stage and proportion of hepatorenal syndrome, serum creatinine and urea at admission and diuresis, amonemia, cardiac manifestations of hyperkalemia, ascites and hepatic encephalopathy in the cirrhotic group at admission, history of hyperkalemia and Sodium polystyrene sulfonate or other resin exchange use at admission.

Reply: Thank you for the suggestions. We are able to respond to most but not all requests. The following new information have been added to Table 1: (1) admission urea and creatinine, (2) breakdown of AKI by KDIGO stage, (3) history of hyperkalaemia, and (4) long-term use of sodium polystyrene sulfonate (prior to admission). With regards to ascites and encephalopathy, they are already captured by the Child-Pugh data. The following could not be provided: [1] hepatorenal syndrome (this is a diagnosis of exclusion and beyond the scope of this study to determine), [2] cardiac manifestations of hyperkalaemia (the correlation between ECG changes and blood potassium level is poor, and serious ventricular arrhythmias were rare), and [3] ammonaemia (this was not routinely measured and depended on the nature of the presentation). While these additional variables may be of interest to readers, we do not believe they are necessary to address the primary aim of this study.
3. In the univariate analysis, the authors should include the center.

Reply: Given the use of a standard insulin-glucose protocol and centralized medical supplies, in a study conducted within the same healthcare network, we do not believe that a significant centre effect is likely. There was no rationale to suspect heterogeneity in the population, treatment, or outcomes among the sites. We feel that such an analysis is unnecessary.

4. It will be interesting that the authors show if the insulin-glucose treatment effectiveness is dependent of the cirrhosis severity according to Child-Pugh score.

Reply: We examined this association as suggested. Firstly, we used ANOVA to compare the means of ΔK+ by Child-Pugh stage and found no significant differences. Secondly, we conducted a nonparametric test for trend by comparing the distribution of ΔK+ quartiles by Child-Pugh categories, and did not find a significant trend for higher ΔK+ with increasing Child-Pugh stage. Thus, we could not demonstrate that a higher Child-Pugh class was associated with incremental resistance to insulin-glucose treatment. Additionally, we found no association between the MELD score and ΔK+ in patients with cirrhosis by linear regression. We have added this information under a new subheading of “Cirrhosis stage and timing of posttreatment K+ test” along with Figure 3, with further comments under the subheading of “Study Strengths and Limitations”.

5. The authors should report the adverse events like hypoglycemia in the 6 hours after the treatment.

Reply: A definition of hypoglycaemia is provided under the “Variable definitions” subheading in the Methods section. We have now included additional information in Table 2 and discuss it under a new subheading of “Glycaemia”. Prior to insulin-glucose treatment, the mean baseline glucose levels for the entire cohort was elevated at 10.7 mmol/L (SD, 5.3 mmol/L), which reflects the high prevalence of diabetes in this population of patients with hyperkalaemia (Table 2). However, baseline glucose was not as high in patients with cirrhosis compared to controls (mean difference 3.2 mmol/L). Posttreatment trough glucose was similar in both groups but the change in glucose from baseline was much smaller in patients with cirrhosis compared to controls (mean difference 4.0 mmol/L). The overall incidence of hypoglycaemia after insulin-glucose treatment was 18.8% and there was weak evidence that patients with cirrhosis had 50% lower odds of hypoglycaemia compared to controls (P=0.07). We mention this interesting finding in the discussion.

6. Figure 2 is not clear. The author should clarify what represent change in potassium.

Reply: We have removed the previous figure and replaced it with a composite figure which we believe demonstrates the main findings with better clarity. The figure legend has been expanded to provide a more verbose description.

Reviewer: 2
Dr. Zubaid Rafique, Baylor College of Medicine

Comments to the Author:

Thank you for inviting me to review this manuscript.

This is certainly an interesting and important study. Overall the objectives are clear and the manuscript is well-written. Following are my concerns:

1. Fig1 - pt enrolment flow diagram shows that control and treatment groups were enrolled at different time periods. Treatment and practice patterns change over time. Is there a reason why the control group was not enrolled over the same time period (vs. only during Jan 2019-Mar2020)? This introduces additional confounders and need to be addressed.

Reply: We believe the reviewer may have misinterpreted the flowchart due to the misleading
phrasing of the figure legend. We have reworded this to hopefully avoid confusion. Controls and cirrhotic patients were not derived from mutually exclusive time periods. Cirrhotic patients were rare, and there was an excess of controls, such that data for control patients from Oct 2016 - Dec 2018 were not used for analysis. In hindsight, we could have randomly sampled control patients instead. However, there was no change to our insulin-glucose protocol during the study period, hence there was unlikely to be practice variation. Furthermore, patients who did not receive the standard protocol treatment were explicitly excluded.

2. Table 2 lists co-treatments. Newer binders (Lokelma and Veltassa are missing from this list. Were they not available at this hospital or data not collected? Potential confounder if not accounted for.

Reply: During the study period, the only exchange resin available was sodium polystyrene sulfonate.

3. Table 2: salbutamol use. Seems like the control group used twice as much as the cirrhosis group (12.7% vs. 6.3%; p=0.11). Although not sig, this is a potential cause of the larger delta K in the control group. This together with the fact the that more cirrhotic pts were on beta blockers which may reduce the efficacy of albuterol could explain the smaller K change. This should be highlighted in the discussion section.

Reply: We have already included all cotreatments including salbutamol (albuterol) in our multivariable regression model as they were significant in the univariable analysis, so hopefully any small difference between the groups have been adjusted appropriately. Similarly, we have adjusted for beta-blocker use in the multivariable model. We also found two coding errors in salbutamol use and corrected these, but there was no change in statistical significance.

4. Total insulin and salbutamol doses should be compared between groups (and not just number of treatments). As we know that hyperkalemia treatment is not standardized and so same number of treatments does not mean same amount of drug.

Reply: We have examined the dose of salbutamol administered during hyperkalaemia treatment and reported it in Table 2. No significant differences were found between the groups. Insulin dose was standardized, and patients who did not receive standard treatment per protocol were excluded. We have also conducted sensitivity analysis on patients who received a second treatment towards the end of their monitoring time.

5. If I understand correctly, the hypothesis is liver disease makes insulin less effective in reducing K. Is it possible to show that worsening liver disease causes increasing insulin resistance and thus poorer K change?

Reply: This is similar to Q4 by reviewer 1, which we have addressed by examining the association between the ΔK+ and both the Child-Pugh and MELD scores. See the additional information in the text and new figure provided.

6. This is an important piece of work and should be published once the above limitations are addressed.

Reply: Thank you for your supportive comment.

Reviewer: 3
Dr. Nathaniel Scott, Hennepin County Medical Center

Comments to the Author:

I thank the authors for their contribution. Interesting and well-written paper. The question is of clinical significance. Appropriate methods for a first investigation into this topic. Use of univariate and multivariate regression supports the analysis.
Three items I would recommend addressing in a revision.

1. The timing of the post-insulin potassium checks. There was some criteria discussed for what would be considered acceptable - 2 checks within 6 hours, at least 1 within 2 hours, I believe. This was a bit confusing and could be more clearly described. It seems that the lower of the values was used, but this should be clarified. Because the potassium lowering effect is rapid and dynamic, the lack of standardized time at which the potassium was checked afterwards is a limitation and a potential confounder. Would recommend reporting the time at which the potassium was checked (relative to the administration of insulin) for the two groups and performing statistical analysis to see if it is different.

Reply: Thank you for your insight. Firstly, we have rephrased and clarified the definition of adequate K+ monitoring under the subheading “Exclusions”. Secondly, we agree that the response to insulin-glucose is dynamic. To address a potential time bias, we evaluated the distribution of time intervals between the end of insulin-glucose infusion and the K+ test which determined the trough level. This was done both graphically (Figure 3) and by non-parametric statistics, and we found neither clinically nor statistically significant differences in testing times between controls and patients with cirrhosis. We have also mentioned this limitation in the discussion.

2. A limitation is that the patients in this study are identified by ICD-10 diagnosis of hyperkalemia. This requires that this diagnosis be coded, and there are likely other patients that had insulins and dextrose treatment of hyperkalemia in these hospitals during this time period that did not receive this code. This may have been the most practical way for the authors to identify this population. Would recommend addressing this limitation in the paper and would ask the authors to speculate if this would result in any selection bias.

Reply: For healthcare funding reasons, health information or medical coders are extremely vigilant in determining a diagnosis of hyperkalaemia. They evaluate the entire medical record and corroborate laboratory values. While it is possible that they may not code mild cases of hyperkalaemia which did not require treatment, it is highly improbable (in our view and experience) they will miss cases of severe hyperkalaemia requiring acute treatment. As we were only interested in patients with severe hyperkalaemia requiring acute K+ lowering, selection bias is likely to be negligible. However, we briefly mention this as a possible limitation in the “Study strengths and limitations” section.

3. Lastly, hypoglycemia is a well-described complication of the use of insulin and dextrose for the treatment of hyperkalemia. The decision about whether to administer insulin/dextrose and the doses of each should involve a considering of the risks/benefits. If the data is available, would be important to report other clinically significant outcomes of this treatment, such as the proportion that experienced hypoglycemia in each group. One could hypothesize that this could be higher in the cirrhosis group.

Reply: This is similar to Q5 by reviewer 1. We have included this additional information in Table 2 and discuss it further under the new subheading of “Glycaemia” and in the discussion. Contrary to the reviewer’s hypothesis, there was weak evidence to suggest that patients with cirrhosis were partially protected from hypoglycaemia, which probably supports the theory of insulin resistance.

VERSION 2 – REVIEW

| REVIEWER       | Robert, Thomas  |
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| Hôpital de la Conception |

| REVIEW RETURNED | 15-Sep-2021 |

| GENERAL COMMENTS | The authors have made the necessary changes and improved the manuscript significantly. But the figures are missing in the version that has been resubmitted. |

| REVIEWER       | Scott, Nathaniel |
| Hennepin County Medical Center |
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| REVIEW RETURNED               |
| 10-Sep-2021                   |

| GENERAL COMMENTS | The authors have adequately addressed the comments mentioned in the first review. The paper answers a question that is relevant using appropriate methods and is well-written and detailed. I commend the authors on their work. |