NPH/regular insulin in the treatment of inpatient hyperglycemia: Comparison of 3 Basal-bolus regimens

Summary of changes

1. The title was shortened to include 13 words, as recommended by the guidelines for manuscript preparation and submission
2. A short running title was included
3. We offered the postcode
4. Author contributions were added
5. A supportive foundation acknowledgement was included
6. A institutional review board statement was included
7. A clinical trial registration statement was included
8. An informed consent statement was include
9. A conflict of interest statement was added
10. A data sharing statement was included
11. The aim of the study was modified according to recommendations
12. A core tip was included
13. Table 1 was provided as a decomposable figure, whose parts are movable and words can be edited
14. Reference numbers were put in superscript
15. The section of comments was included
16. Pub Med citation numbers and DOI citation were added to the reference list
17. All authors were added in the reference list
18. The manuscript was modified according to the Guidelines and Requirements for Manuscript Revision-Randomized Controlled Trial.

RESPONSE TO REVIEWERS

Reviewer's code: 02476743
Reviewer's country: Taiwan

1. **Why no controlled group was used in this study?**

Response: The twice daily regimen should be used as the control group. Some comments were added:

Introduction, paragraph 4: "Current guidelines do not specify whether the NPH dose of insulin should be administered in a once daily, twice daily o three times daily regimen during hospitalization. The twice daily regimen has been traditionally used in previous clinical trials as the standard regimen of reference, suggesting it to be the most physiologic form of administration."

Methods, study protocol and treatment, paragraph 2: "The twice-daily regimen was also included as the reference regimen, since it has been traditionally used in previous trials when NPH/Regular insulin is administered in hospitalized patients. "

2. **Please estimate the final power in this study.**

Response: The sentence "Despite the fact that 16% of the randomized patients were lost during follow up, the minimum of 93 subjects to maintain the statistical power of our study was accomplished. In addition, only patients who completed the study were included for the analysis. We believe that in spite of this limitation, our findings provide reliable information to draw conclusions." was added in discussion, paragraph 6.

3. **More discussion regarding the policy implications of their findings would be important for the use of methodology in health policy making.**

A comment was included in the conclusions: "Despite its limitations, our findings could be useful for changing algorithms for the treatment of inpatient hyperglycemia in addition

to current health policies. Further studies are needed to estimate whether NPH insulin in a once-daily regimen can be incorporated as an option in certain populations among the hospitalized patients."

4. **The repeated measurements should be better than ANOVA or Kruskal Wallis test in this study**.

Response: A comment was added in methods, outcome measures, paragraph 1 in order to clarify that the mean glucose values were established as the average of daily repeated measurements taken each day during hospitalization: "Mean overall, fasting and random, glucoses were also used to assess differences in glycemic control between the three regimens. They were established as the average of daily repeated measurements taken each day during hospitalization. "

Furthermore, a comment was also included in the discussion section, paragraph 6: "We are aware that the comparison of repetitive measurements could be a better strategy for statistical analysis, however we decided to use average glucose levels since this is the way it has been presented in previous studies that compare different schemes of treatment of inpatient hyperglycemia."

Reviewer's code: 03490863
Reviewer's country: Russia

1. **To assess the correctness of the conclusions more detailed information about the included patients should be provided.**

    a. **Which oral antidiabetics had been used before and during the study in each group?**

Response: The sentence "Metformin and glibenclamide were the only oral antidiabetics used by the patients prior hospitalization. These drugs were drugs were suspended during hospitalization." was included in results, paragraph 1.

    b. **What kind of infections had the patients?**

Response: The sentence "Pneumonia was the most common cause of infection, followed by urinary tract infections and diarrhea." was included in results, paragraph 1.

    c. **How much subjects with sepsis were included?**

Response: The sentence "None of the subjects with sepsis were included." was included in results, paragraph 1

    d. **What was the prevalence of diabetic complications in each treatment group?**

Response: The sentence "Diabetes related chronic complications were not evaluated in this study." was included in results, paragraph 1.

2. **As it is shown in Table 2, patients in the once-daily regimen had a shorter duration of diabetes (p=0.01) and were less prone to insulin use before hospitalization (p=0.01). The proportion of patients with unknown history of diabetes was substantially greater in this group as compared to others (p=0.01). In once-daily regimen group only, none of the patients received combined treatment with insulin**

and oral antidiabetics prior to hospitalization. Besides, proportion of patients with neoplasm was larger, and proportion of patients with infections was smaller in this group. Rate of hypoglycemia tended to be higher, meantime insulin dose at the event was lower in once-daily regimen group (Table 4), indicating greater insulin sensitivity.

a. **These features may explain the better glycemic response and lower insulin dose in once-daily regimen group. Obviously, the differences in characteristics of the patients have not been overcome by randomization. This limitation needs to be explained.**

Response: The limitation was included in the discussion section, paragraph 6: "As it is shown in Table 2, patients in the once-daily regimen had a shorter duration of diabetes and were less prone to insulin use before hospitalization. Additionally, the proportion of patients with unknown history of diabetes was substantially greater in this group as compared to others, the rate of hypoglycemia tended to be higher and the meantime insulin dose at the event was lower, indicating probable greater insulin sensitivity. These features could explain the better glycemic response and lower insulin dose in once-daily regimen group instead of the once-daily regimen itself."

A comment was also included in the conclusions: "Whether this superiority in glycemic control and insulin dose was related to greater insulin sensitivity among the study subjects in the once-daily regimen needs to be reassessed in further studies."

b. **The main conclusion of the study ("A basal-bolus regimen of insulin NPH given once-daily together with regular insulin resulted in better glycemic control with similar rates of hypoglycemia and lower insulin requirements in non-critical hospitalized patients") seems to be inappropriate and should be reviewed.**

Response: The main conclusion of the study was reviewed and changed:

"NPH insulin administered in a once-daily regimen resulted in improvement in glycemic control with similar rates of hypoglycemia compared to a twice-daily and a three times-

daily regimen. Further studies are needed to evaluate whether this regimen could be implemented in all hospitalized patients with hyperglycemia."

3. **The median duration of treatment was 6 (2-14) days, and the median hospital stay was 8 (2-36) days. A short period of treatment may not be sufficient for titration of insulin dose and achieve of glycemic target in some patients. Short follow-up should be clearly mentioned as a limitation of the study in Discussion section.**

Response: The authors don´t see the short period of follow up as a limitation. A comment was included in the discussion section, paragraph 6: "Even though subjects were treated with the insulin regimen during the whole hospitalization, the median duration of days for follow up in our study was 6 (2-14) days. This period of maximum 14 days of follow up permitted an adequate titration of insulin dose with achievement of glycemic target in all patients and avoided bias linked to long hospital stay related complications."

4. **Abstract is needed to be much more comprehensive.**

The abstract was modified according to the Guidelines and Requirements for Manuscript Revision-Randomized Controlled Trial. It was shortened from its original version, which is why it only includes the main findings of the study.e

5. **Type of diabetes in included patients should be specified.**

Response: The sentence "85 of them with known type 2 diabetes mellitus" was included in results, paragraph 1.

Minor revisions

1. **There are some grammatical mistakes throughout the text.**

Grammar was reviewed by Dr. Sergio Lozano-Rodríguez MD

2. **Table 3 and 4 headers should be clarified.**

Response: Headers were clarified

Table 3: Glycemic control among subgroups. Proportion of patients that achieved glycemic targets during the whole follow up.

Table 4: Rate of hypoglycemia among the study groups during the hospitalization