

Comments Reviewer 1

This mini review focuses on the management of blood glucose in the ICU, which is very important particularly in terms of increased hospital mortality. The contents sound interesting and are worthy of publication, because the evidence is limited. However, some issues below should be addressed by adding some discussion or depicting a new table or figure.

Response: We appreciate the reviewer's comments. New changes were made and added at the end of the article in "FUTURE APPROACHES" part. Please see responses below.

1 Most patients in the ICU may undergo non-oral parenteral alimentation. Such non-oral alimentation aggravates glucose control, especially in case of total parenteral nutrition including high amount of glucose, which directly rises blood glucose level.

Response: Thanks for the comments. This point was addressed in page 11 in "FUTURE APPROACHES"

2 By contrast, baseline malnutrition and underweight may predispose to higher incident of hypoglycemia compared to overweight or obesity.

Response: This point is very important as we are not only discussing hypoglycemia events, but hyperglycemia states too. We made emphasis on hypoglycemia since is more labile and dangerous, but thanks for the point, is now added at page 11 in "Future approaches".

3 Age is an important factor that should be considered for intensive insulin therapy, because the incident of hypoglycemia is higher in older people than younger people.

Response: Although, we didn't mentioned the weight or age, we mentioned some comorbidities such as diabetes mellitus, which is an important result that is very related to the afore mentioned factors. We added this to "FUTURE APPROACHES" on page 11.

Comments Reviewer 2:

This is a review article regarding blood glucose control in the ICU. Although the review was concisely written, the purpose of the review was unclear. The clinical message of the authors was not clearly described in the abstract as well as core tips. Unfortunately, this article seems to add little information in this field.

Response: We appreciate the reviewer's comments. We have tried to address the concerns by adding the section on future approaches and have tried to make the abstract more palatable. This article is a mini-review that addresses important situations regarding glycemia in ICU, which is an essential situation that every clinician should take into consideration in managing hypoglycemic/hyperglycemic state in critically ill patients. Many hospitals have taken into account many of this aspects too in order to improve some of the technology and devices to have a better control and monitoring in critically ill patients. This article supplements the information regarding cost-effectiveness comparison, glucose monitoring and insulin therapy (see table for comparison) and future approaches.

Comments Reviewer 3

The authors focused on the topic of appropriate blood glucose control that was ignored by many intensive care unit (ICU) clinicians by searching PubMed™. It is difficult to control blood glucose at optimal levels without hyperglycemia or hypoglycemia. Both of them would have a significant effect on clinical outcomes as well as hospitalization expenses. The authors concluded several guideline recommendations on glucose

control and compared different management criteria for blood glucose in critical patients. They also introduced the development of glycemic monitoring methods of critical patients. Tight and moderate glycemic control had a distinctive effect on patients with different primary conditions. At the end of this article, the authors put forward the requirements for ICU clinicians, and they believed that blood glucose monitoring and treatment would be more scientific and standardized. The authors failed to provide detailed information, which was necessary for readers to understand this topic in many aspects maybe due to the short length of the review article.

1. The authors should pay more attention to the subtitle of this review article. The subtitle 'GLUCOSE MONITORING AND INSULIN THERAPY IN CRITICALLY ILL PATIENTS' and 'CURRENT GLYCEMIC MONITORING BG TECHNOLOGY' seem very similar and may confuse the readers. The former mainly focus on comparing differences in outcomes from a different level of treatment objectives while the later-described blood glucose monitoring methods. Similar to this problem, in Part 'BLOOD GLUCOSE CONTROL IN DIABETIC PATIENTS IN THE ICU', the authors introduced blood glucose control not only in diabetic patients. However, they compared the blood glucose control level of patients with diabetes and non-diabetic critical patients in detail.

Response: We appreciate the reviewer's comment. We have changed the topic to "Insulin Therapy in Critically Ill Patients and Newer Technologies for Blood Glucose Monitoring" for more clarity

2. When it comes to cost-effectiveness, the authors described two kinds of blood glucose methods and advocated the second method due to reduced nursing staff fatigue and shortened treatment time for an abnormal level of blood glucose. However, in Part 'cost-effectiveness', there were short of detailed comparisons. The cost-effectiveness of different levels of treatment objectives or different guideline recommendations should be compared.

Response: Newer information was added to “cost-effectiveness” in page 11, for further comparison.

3. Would be better to put the Part ‘complications’ into Part ‘introduction’. It is illogical to introduce clinical complications after the introduction of a significant number of attempts to find the best way to monitor and control blood glucose.

Response: Agree with the reviewer’s comments. “COMPLICATIONS” subtitle was moved to the introduction.

4. The authors studied only one electronic database to screen literature. Moreover, they excluded articles, which could only get abstract in PubMed. In order to make the review article more comprehensive, another influential electronic database should be utilized.

Response: Appreciate reviewer’s comments. Since this is mini-review rather than systematic review/meta-analysis, we felt that pubmed does have majority of the key indexed article and many re-direct to another database (Ex. Elsevier - Sciencedirect) would suffice. Though point well taken.

5. The article mentioned ‘critically ill patients’ many times without giving a clear definition of it. Whether a patient is a critically ill patient with severe hyperglycemia as a primary disease? The patient who was repeatedly injected with insulin by mistake is also in danger of life.

Response: By critically ill patients we meant every patient in the ICU with any life-threatening multisystem process independently from the etiology, of course we made emphasis in diabetic patients since they are more susceptible to glucose fluctuations compared with the rest of the patients. We added information at page 5 regarding the etiology.

6. The mean blood glucose has an interesting distinction between surgical ICUs and the medical ICUs. Please try to make some explanations of this distinction.

Response: Appreciate the reviewer's comments. Changes were made in "GLUCOSE MONITORING AND INSULIN THERAPY IN CRITICALLY ILL PATIENTS" on page 8-9. Study on 210 patients in 4 different ICUs, monitoring BG was followed by management with a computerized insulin infusion program (CIIP) programmed to a moderate glycemic range of 120-160 mg/dL in surgical ICU's and 140-180 mg/dL in medical ICU's. The targeted ranges were different, that explains the difference in the mean BG which was on the target on both types of ICU's. Surgical ICU: mean BG 147 mg/dL (120-160 mg/dL) and medical ICU: mean BG 171 mg/dL (140-180 mg/dL).

7. Authors should provide more information for controlled trials done by Van den Berghe and associates for a better understanding of experimental results. Are patients in the experience group treated with non-rigorous glucose control?

Response: We appreciate the reviewer's comments. Changes were made in "INTRODUCTION" ref 2. regarding Van den Berghe study.

8. The authors should further clarify the features of COIITSS study. Was the COIITSS study multi-center or single-center? How many patients were selected?

Response: changes were made in "GUIDELINE RECOMMENDATIONS ON GLUCOSE CONTROL" in COIITSS study ref 21 " COIITSS study investigators performed a multicenter randomized clinical trial involving 509 adult patients with septic shock, revealing no significant mortality in patients with a target BG of 80 to 110 mg/dL as compared to those with a target BG of 150 mg/dL."

9. In order to facilitate understanding, the authors should briefly introduce the method of calculation for a total time below 70mg/dL in intermittent groups in the trials run by Preiser et al.

Response: Appreciate the reviewer's input and agree. We added info pertaining to this on page 10 : "TB70 (time spent with BG <70mg/dL) was calculated with continuous glucose monitoring device, and resulted in 0.4% +/- 0.9% vs 1.6%+-3.4% ($p < 0.05$) in intermittent glucose monitoring group. [35]"