

## AACE Patient Safety - Editorials

### **The NICE-SUGAR Study on Intensive versus Conventional Glucose control-The Importance of Patient Safety in Achieving the Desired Outcomes**

2009-03-25 15:56:43

By: Dr. Richard Hellman

The long-awaited NICE-SUGAR trial results have just been published on-line in the New England Journal of Medicine, together with an excellent editorial by Inzucchi and Siegel. The ADA and AACE have also released a joint statement. In their very thoughtful statement, they expressed a concern that providers of care will take the published results of the NICE-SUGAR study and conclude incorrectly that they can afford to be more complacent about uncontrolled hyperglycemia.

Their concern is justified. Some of the initial news commentary stated that the NICE-SUGAR showed that that intensive insulin therapy to achieve glucose control increases mortality in critically ill patients and may be dangerous. However, it is best to look carefully at what the actual data is.

The data provided by the NICE-SUGAR article shows that the odds ratio for death in the intensive control group was 1.14, with a 95% confidence interval of 1.02 to 1.28 and a P=0.02. The severe hypoglycemia rate (Glucose  $\leq$ 40mg/dl or 2.2mmol/L) was 6.8% in the intensive-control group and only 0.5% in the conventional group. On the surface it would seem that the results are unequivocal. But that would be an incorrect conclusion.

To begin with, the mean glucose level in the conventional-control group was 144mg/dl, as opposed to the intensive therapy group glucose level of 115mg/dl. The difference is not large, only a mean of 29mg%. The control in the conventional-control group was in the range of only relatively modest levels of hyperglycemia, much lower than the control groups in many other studies, which were often over 200mg%. . In addition, there were a significant number of patients, 74, whose vital status data was unknown, and a significant amount of reassignment of patients as noted in the paper. The 14% increase in death rate in the intensive group could be possibly explained by other factors not available in the analysis.

But a more compelling reason to be careful about the analysis is the fact that the NEJM article gives very little information about THE FREQUENCY THAT THE ALGORITHMS WERE DONE AS PLANNED. The algorithms used for the insulin infusions were constructed so the insulin infusion rate varied widely and the rate would change from 0 units/hr to 1, 2, and 4, units /hour in response to the glycemic levels noted. With this type of infusion algorithm, it is imperative to not let the interval in between the glucose determinations be excessively long, since otherwise the swings in glucose levels would be very rapid and large in amplitude.

In fact, in the report of their first 100 hypoglycemic events, the NICE-SUGAR study

group, as reported on their ANZCA web-site, the most common adjudicated cause of hypoglycemia was clinician error, which was 37% of the group. They defined clinician error as either failure to follow the computerized treatment algorithm or inappropriately infrequent blood glucose monitoring. The next most common event, at 24 % of the adjudicated causes, was decreased nutritional intake. Each of these causes are a failure to follow the agreed upon plan.

So, is the problem of the failure of the NICE-SUAR study to show positive results in the intensive insulin therapy group that the target glucose level was set too low, or is it that the plan was good, but was carried out sub-optimally? While my opinion is that the reasons for the outcomes were complex, it is clear that in a sub-optimally conducted trial, even if the subjects were randomly assigned, a deviance from the plan of the trial weakens or limits the strength of the conclusions that should be drawn.

Yet, I think there is much about the NICE-SUGAR study that makes it an important addition to the literature. It suggests that in very ill patients, particularly patients on ventilators, and with marked severity of illness, that patients may be very vulnerable to hypoglycemia, and this much be scrupulously avoided. Also, the effects of early severe hypoglycemic episodes may be delayed, as some of the excess mortality was later, and may have represented subtle effects not initially noted in the ICU.

Also, the fact that a mean glucose level of 144mg% was associated with outcomes in an ICU that was not worse than those with lower glucose levels suggest that a target in this range may be safe.

But their own data on hypoglycemia strongly suggests that it is crucial to be sure that the algorithm is being carried out correctly for optimal results. And data from both Keukoven, 2008, Blaha, 2009, and Van Den Berghe, 2008, all point out that the training of a nursing team who is in charge of actually overseeing the insulin infusions is crucial. There is a need to provide adequate numbers of trained personnel, and both education and continuing oversight. Quality improvement in this setting depends upon reviewing the work product and improving what is less than optimal. . In the editorial by Inzucchi and Siegel, they correctly point out that in many hospitals, a seamless and automatic use of insulin infusions has developed. These efforts have already resulted in a small but growing literature on the successful use of insulin infusions. More data will certainly be welcomed, for the NICE-SUGAR study is important, but far from definitive.

1. The NICE-SUGAR Investigators, Intensive versus Conventional Glucose Control in Critically Ill Patients, NEJM, 360;13 March 26, 2009, pgs 1283-1297
2. Inzucchi, SE, and Siegel, M., Glucose Control in the ICU-How Tight is Tight?, NEMJ, 360;13, March 26, 2009, pgs 1346-9
3. Joint Statement of the ADA and AACE on the NICE-sugar study, Press Release, March 24, 2009, on [http://media.aace.com/article\\_display.cfm?article\\_id=4886](http://media.aace.com/article_display.cfm?article_id=4886)

<http://www.aacepatientsafetyexchange.com/editorial/index.php?id=22>