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EDITORIAL

Intensive Insulin Management of Inpatient Hyperglycemia: Where Are We?

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Hyperglycemia that develops acutely due to illness is associated with poor patient outcomes in hospitalized inpatients, especially those critically ill in the intensive care unit (ICU).[1–8] In fact, those without a prior diagnosis of diabetes and therefore newly found to have hyperglycemia have worse outcomes than those who have a prior diagnosis of diabetes.[1,2,4,6–8] Many mechanisms have been put forward to explain the adverse outcomes related to hyperglycemia, including the release of counter-regulatory hormones, increased lipolysis with free fatty acid release, the release of inflammatory cytokines and growth factors, increased reactive oxygen species with oxidative stress and altered immunoglobulin, and neutrophil phagocytic function.[9–11]

The practical importance of this was brought home by Furnary et al.[12,13] who showed that glycemic control using 3 days of intensive intravenous (IV) insulin therapy of diabetic patients undergoing cardiac surgical procedures was able to reduce significantly the risk of deep sternal wound infections and mortality and to bring these adverse outcomes to the same levels as those of nondiabetic patients. However, the benefits of intensive insulin therapy are not limited to those with diabetes and extend to those with critical illness-induced hyperglycemia. In a landmark, randomized, prospective study from Belgium, van den Berghe et al.[14] showed that the use of an intensive IV insulin protocol designed to maintain serum blood glucose 80 mg/dL to 110 mg/dL significantly decreased morbidity and mortality following admission to the surgical ICU (SICU). Of note, only 13% of the individuals in the study had a previously known diagnosis of diabetes, showing that hyperglycemia was common following SICU admission and glycemic control was beneficial regardless of diabetes status.[14]

These impressive benefits[12–14] led to the call for improved glycemic control in the hospital with glucose targets similar to those used in the Belgian study.[15] The development of protocols for such treatment proceeded rapidly.[16,17] A meta-analysis that reviewed 14 trials through May 1, 2006 of patients in SICUs showed a 31% reduction in mortality with intensive therapy, albeit at the expense of a substantially increased risk of hypoglycemia.[18] Our own studies[19] using 1 day of continuous insulin infusion followed by subcutaneous basal/bolus insulin for all hyperglycemic patients following coronary artery bypass surgery showed results similar to those of Furnary et al.[12,13]

Subsequently, 3 large, multicenter studies of patients in medical ICU (MICU) and SICUs, the VISEP, NICE-SUGAR, and GLUCONTROL studies, failed to show the benefit of intensive insulin therapy on mortality and all had very high rates of hypoglycemia.[20–22] The VISEP[20] study was stopped prematurely because of excessive hypoglycemia in the intensive treatment arm and the GLUCONTROL study was stopped prematurely because of multiple protocol violations.[22] The NICE-SUGAR study actually showed an increased mortality in the intensively treated group[21] but the target range for their control group was 140 mg/dL to 180 mg/dL rather than 180 mg/dL to 215 mg/dL and this likely accounted for the better mortality in their control group compared to other studies. Van den Berghe et al.,[23] in a design similar to their earlier one in the SICU, found that intensive insulin therapy in the MICU resulted in significant reductions in new onset renal injury, MICU and hospital length of stay, and an improved ability to wean off mechanical ventilation; however, no improvement in mortality was found except for those whose MICU stay was >3 days duration. In a post hoc analysis of their combined SICU and MICU studies, van den Berghe et al.[23] found that a glucose target of 110 mg/dL to 150 mg/dL accounted for about 75% of the mortality benefit with a low risk of hypoglycemia.[24] A recent meta-analysis that included data on 13,567 patients from 26 trials, including the NICE-SUGAR study, concluded that although overall there was no mortality benefit from intensive insulin therapy there was benefit in the SICU but not in the MICU or mixed ICU units.[25]

As a result of these later studies, new recommendations from the American Association of Clinical Endocrinologists and the American Diabetes Association state that for optimal risk/benefit, the overall goal of inpatient treatment for most patients should be 140 mg/dL to 180 mg/dL, although a range of 110 mg/dL to 140 mg/dL may be appropriate for some patients.[26] Stressed in this Consensus Statement is the need for experienced practitioners and systems to provide optimal implementation of protocols so as to provide adequate glycemic control without an undue amount of hypoglycemia. We have found that active individual patient management by experienced nurse practitioners who can modify existing protocols as needed provides better glycemic control with less hypoglycemia than nursing personnel

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TABLE 1. Key Points in Inpatient Glycemic Management

Measure HbA1c on admission to aid in discharge planning
Start insulin infusions in postoperative and other unstable patients if blood glucose >180 mg/dL on 2 or more occasions
Begin IV continuous insulin infusion using validated protocols
Glucose target: 140-180 mg/dL*
When converting from IV to subcutaneous insulin
Give 80% of stable IV dose as glargine insulin
Give 10% of glargine dose as rapid acting insulin
Then stop insulin infusion
If starting with subcutaneous insulin without prior insulin infusion
Give 50% as long-acting insulin (glargine or detemir)
Give 50% as rapid-acting insulin, divided into 3 for the 3 meals

Abbreviations: HbA1c, glycosylated hemoglobin; IV, intravenous.
*Lower target of 110 mg/dL to 140 mg/dL may be appropriate in some settings.

adhering to a protocol without taking into account the myriad of factors affecting patients daily.[16]

Although hypoglycemia is certainly to be avoided and has been associated with increased mortality,[6,27] Kosiborod et al.[7] showed that mortality in hyperglycemic patients following an acute myocardial infarction was not related to insulin-induced hypoglycemia but to hypoglycemia unassociated with insulin use. In the latter case, the hypoglycemia is generally attributable to shock, sepsis, malnutrition, liver failure, renal failure, or multiorgan failure.

One of the potential hurdles to achievement of glycemic control in the critically ill is the labor-intensive changes in patient care policies necessary to attain these goals. Particular concern lies in the ability of inpatient care providers to develop and implement successful insulin protocols. Intravenous insulin administration is effective and appropriate in the ICU and some non-ICU settings, but administration of insulin subcutaneously is less nursing intensive and a more familiar hyperglycemia treatment option. However, glycemic control with subcutaneous insulin is only achieved using basal/bolus regimens and not with simple "sliding-scale" regimens that omit basal insulin and attempt to treat rather than prevent hyperglycemia.[28]

In this issue of the *Journal of Hospital Medicine*, 3 articles deal with some of the practical aspects of inpatient hyperglycemia management. In ICU patients on continuous IV insulin infusions, Newton et al.[29] demonstrated improved glycemic control without an increase in hypoglycemia when using a computer-guided insulin algorithm using a handheld device (Glucommander) compared to a paper algorithm. A previous publication in JHM showed that when continuous insulin infusions were used on the regular hospital floors outside of the ICU, Smiley et al.[30] found that 67% of patients achieved the targeted goal of <150 mg/dL by day 2. Wesorick et al.[31] found that simply educating floor nurses as well as physicians and using standardized insulin protocols resulted in improved glycemic control and less hypoglycemia on inpatient services outside of the ICU. In the third paper, Ramos et al. found that those with glycosylated hemoglobin (HbA1c) levels >6.0%, a prior history of diabetes, or chronic steroid use did better with basal insulin than with no basal insulin when converting from insulin infusions.[32] In contrast to their using only 40% of the stable insulin infusion rate for their basal dose, we found that 80% worked better.[33] We also learned the hard way that overlap of the infusion by 2 hours to 4 hours after giving the basal insulin subcutaneous dose is just not carried out by the treating team because of timing and practical considerations. We now just give a dose of rapid acting insulin equal to 10% of the basal insulin dose at the time of the injection of the basal dose; this allows for the immediate cessation of the infusion without loss of glycemic control (Table 1).

Intensive insulin treatment in the ICU clearly results in better outcomes when compared to letting glucose levels remain greater than 200 mg/dL. A glucose target range of 140 mg/dL to 180 mg/dL provides improved mortality and morbidity with a low risk of hypoglycemia and is suitable for most hospitals. A more aggressive target range of 110 mg/dL to 140 mg/dL provides further improvement but increases the risk of hypoglycemia and would only be appropriate for those institutions with considerable experience with such therapy and demonstrated low rates of hypoglycemia. Work is still needed on devising the ideal treatment algorithm, regimens for conversion from IV to subcutaneous insulin, and discharge planning. However, the most important part of patient care we have found is the insertion of an intelligent and experienced brain between the patient and the insulin protocol.

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