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Slow Deadoptation of a Strategy: Was Tight Glycemic Control Truly Impractical?

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Hyperglycemia is a prevalent scenario in critically ill patients. Hyperglycemia is associated with many adverse outcomes, including immune disorder, oxidative stress, susceptibility to infection, and endothelial dysfunction. Its impact is believed to be independently associated with increased mortality because it enhances the inflammatory responses. Some randomized controlled clinical trials have attempted to determine whether intensive insulin therapy targeted on establishing normoglycemia could benefit septic patients. Initial studies of adjustable insulin infusions to decrease blood glucose levels raised interest in inpatient glycemic control strategies (1,2), and several organizations called for implementing intensive insulin therapy (IIT) strategies using adjustable insulin infusions titrated to strict glycemic targets in the intensive care unit. Despite the early evidence of benefit from IIT (3-6), many subsequent trials, including the largest IIT trial to date, have not found a consistent benefit (7).

Niven et al., in their article (8), evaluated glycemic control in critically ill patients before and after the publication of clinical trials, highlighting the fact that it was initially suggested that tight glycemic control reduced mortality (i.e. LEUVEN I study(6)), but subsequently it was suggested that tight glycemic control increased mortality (i.e. NICE SUGAR trial (7)). Before the publication of Leuven I, 17.2% (95% CI, 16.2%-18.2%) of ICU admissions had tight glycemic control, 3.0% (95% CI, 2.6%-3.5%) had hypoglycemia, and 40.2% (95% CI, 38.8%-41.5%) had hyperglycemia. After the publication of Leuven I, there were significant increases in the relative proportion of admissions with tight glycemic control (1.7% per quarter; 95% CI, 1.2%-2.3%; $P < .001$) and hypoglycemia (2.5% per quarter; 95% CI, 1.9%-3.2%; $P < 0.001$) and decreases in those with hyperglycemia (0.6% per quarter; 95% CI, 0.4%-0.9%; $P < 0.001$). Following the publication of NICE-SUGAR, there was no change in the proportion of patients with tight glycemic control or hyperglycemia. There was an immediate decrease in the relative proportion of patients with hypoglycemia (22.4%; 95% CI, 13.2%-30.1%; $P < 0.001$) but no subsequent change over time. The authors

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reported that little or no deadoption from tight glycemic control was achieved following NICE SUGAR trial (1).

It should be considered that there are fundamental differences between LEUVEN and NICE SUGAR trials. First, the level of therapy compliance in LEUVEN study was 70% compared to less than 50% in NICE SUGAR trial. Unsurprisingly, studies having managed to adequately achieve the blood glucose target have been associated with a reduced mortality compared to those not succeeding in therapy compliance. Second, in NICE SUGAR study, a variety of sampling sites and glucose meters were allowed most of which have recently been shown to be unsuitable for this purpose. Third, feeding strategies differed in two studies; in NICE SUGAR study feeding relied almost exclusively on the enteral route whereas in LEUVEN study, most of patients received supplemental parenteral nutrition which could be directed to a better response to insulin therapy. Fourth, most of the studied subjects in NICE SUGAR study were medical patients whereas in LEUVEN study, most of the studied subjects were surgical patients; these two different target groups would have had different responses to insulin therapy. Finally, normoglycemia was compared with distinctly different control targets (10-12 mmol/l in LEUVEN vs. 8-10 mmol/l in NICE SUGAR studies) which would have led to completely different results. As can be observed, there are numerous fundamental differences between these two studies which could have contributed to different outcomes. These obvious differences would definitely contribute to the unwillingness of the physicians for deadoption from tight glycemic control protocol. Further trials are required to evaluate this complex intervention which is occasionally incompletely implemented in recent trials.

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