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# Tight Glycemic Control in Critically Ill Adults

Simon Finfer, MBBS, FJFICM

Anthony Delaney, MBBS, FJFICM

**I**N CRITICAL CARE MEDICINE, IT IS UNLIKELY THAT ANY single study has had the influence to match that of the study by van den Berghe et al<sup>1</sup> of intensive insulin therapy in surgical intensive care patients. Published in 2001, the study reported that targeting normoglycemia in ventilated patients in a surgical intensive care unit (ICU) reduced the risk of in-hospital death by one-third. Although the size of the treatment effect seemed improbable, the underlying concept had face validity as improved glycemic control had been proven beneficial in other patients with severe acute illness.<sup>2</sup> As a result, tight glycemic control in critically ill adults is now recommended by numerous organizations including the American Diabetes Association<sup>3</sup> and the Institute for Healthcare Improvement.<sup>4</sup> In this issue of *JAMA*, Wiener and colleagues<sup>5</sup> report a meta-analysis of studies examining tight glycemic control in critically ill adults; their conclusions, that tight glycemic control does not significantly reduce in-hospital mortality, may surprise many clinicians.

Possible explanations for the discordant results of the study by van den Berghe et al<sup>1</sup> and the meta-analysis by Wiener et al<sup>5</sup> are that the meta-analysis is flawed, the studies that form the basis of the meta-analysis are flawed or inherently different, or the findings of the study by van den Berghe et al<sup>1</sup> occurred due to random chance or as a result of another unique factor interacting with tight glycemic control.

Wiener et al<sup>5</sup> sought to identify studies in which critically ill adults were randomly assigned to receive either tight or standard glucose control and that reported either in-hospital or short-term mortality, new need for dialysis, or septicemia as outcomes. They identified 29 studies that included 8432 patients and reported 1869 deaths. The overall relative risk of death for those treated with tight glucose control was 0.93 (95% confidence interval, 0.85-1.03). Additionally, subgroup findings for trials that targeted a blood glucose concentration of less than 110 mg/dL and subgroups selected according to the type of ICU (surgical, medical, or medical-surgical) did not demonstrate a significant reduction in mortality.

See also p 933.

As with any individual randomized controlled trial, subjecting the conduct and results of a meta-analysis to structured critical appraisal is a key step in deciding whether to accept the findings and modify clinical practice.<sup>6</sup> The study by Wiener et al<sup>5</sup> satisfies the major criteria for a valid meta-analysis; it addressed a focused clinical question, used an appropriate search strategy, was unlikely to have missed important studies, and the quality of the studies was assessed using a recognized scoring system.<sup>7</sup> The meta-analysis thus appears well-conducted and provides a timely overview of the evidence for and against the adoption of tight glycemic control.

The inferences that can be drawn from a meta-analysis are dependent on the quality of its constituent trials. Wiener et al<sup>5</sup> used the Jadad scale<sup>7</sup> to assess the quality of the trials. This scale assesses aspects of trial design (randomization, allocation concealment, blinding, and attrition) that are important for generating unbiased results; it does not assess other trial characteristics that are critically important when studying tight glycemic control in critically ill patients.

Maintaining the blood glucose concentration of critically ill patients within a range of 80 to 110 mg/dL (4.4-6.1 mmol/L) is difficult to achieve; clinical studies targeting that goal report 40% to 80% of blood glucose readings fall outside the target range.<sup>8-10</sup> Consequently, the success of the investigators in achieving blood glucose targets becomes a critical quality marker for individual studies and the potential benefits reported by van den Berghe et al<sup>1</sup> should only be discounted if other studies achieve similar glycemic control without a demonstrable reduction in mortality. However, comparing studies is difficult because there is no accepted standard for reporting of glycemic control.<sup>11</sup> The studies by van den Berghe et al<sup>1,12</sup> report only the mean morning blood glucose concentration; other investigators advocate reporting the percentage of time patients' blood glucose concentration is within the target range,<sup>10</sup> or the area under the curve above the upper limit of the target range (the hyperglycemic index).<sup>13</sup>

**Author Affiliations:** Critical Care and Trauma, The George Institute for International Health (Dr Finfer); University of Sydney, and Intensive Care Unit, Royal North Shore Hospital (Drs Finfer and Delaney), Sydney, Australia.

**Corresponding Author:** Simon Finfer, MBBS, PO Box 443, Wahroonga, Sydney, NSW 2076, Australia (sfinfer@george.org.au).

An additional complication is the claim that both the absolute concentration and the degree of variability in blood glucose concentration are important because both are related to mortality.<sup>14</sup> As yet, it is unclear whether increased blood glucose variability is a marker of severity of illness that is not corrected for by standard multivariate analyses or alternatively, whether achieving both a low and stable blood glucose concentration is necessary to reduce mortality.<sup>15</sup> To complicate matters further, even within the context of clinical investigations, bedside testing of blood glucose concentration in critically ill patients may be inaccurate,<sup>16,17</sup> and it is unclear how such inaccuracy affects tight glucose control both within clinical trials and in clinical practice.

Leaving aside the issue of measuring and reporting glycemic control, a further unanswered question is whether there is an interaction between tight glycemic control and the administration of intravenous glucose and parenteral nutrition. The patients in both of the studies by van den Berghe et al<sup>11,12</sup> received large doses of intravenous glucose averaging approximately 160 g/d as part of a predetermined feeding regimen.<sup>18</sup> This is far from universal practice and contrasts with an estimated 12.2 g of parenteral glucose administered per day in ICUs in Australia and New Zealand.<sup>19</sup> Consistency in describing nutritional practices in future study reports may clarify whether tight glycemic control is only effective in patients who receive large doses of intravenous glucose.

As discussed by Wiener et al,<sup>5</sup> one interpretation of their meta-analysis is that it had insufficient power to demonstrate the statistical significance of a clinically important difference in mortality. The observed absolute reduction in mortality with tight glycemic control was 1.7%, meaning that 58 patients would have to be treated to prevent 1 death, a number that most clinicians would probably consider reasonable. However, the upper limit of the 95% confidence interval for relative risk of death was 1.03, which is consistent with tight glycemic control causing a small increase in mortality. Therefore, whether tight glycemic control is beneficial or harmful is uncertain, and given the consistent finding that tight glycemic control substantially increases the risk of severe hypoglycemia, the possibility that tight glycemic control is harmful cannot be ruled out. Further data on the benefits and harms of tight glycemic control in critically ill patients will be available once the NICE SUGAR study, a pragmatic study of tight glycemic control being conducted in 41 hospitals in Australia, New Zealand, and Canada and at the Mayo Clinic in the United States, is completed. Recruitment of 6100 participants will be completed in August 2008 and the results should be available in the first half of 2009. Because approximately 30% of the study population is expected to die within the 90-day follow up period, NICE SUGAR is anticipated to report approximately 1800 deaths and should substantially increase the power of any future meta-analysis.

While awaiting the results of the NICE SUGAR study, how should clinicians and policy makers interpret the results of the meta-analysis by Wiener et al?<sup>5</sup> Given the lack of an agreed standard for glycemic control and incomplete reporting in most trials, and that the effect of blood glucose variability and inaccurate bedside measurement of blood glucose remain unclear, the meta-analysis is best viewed as a large “effectiveness” study. The meta-analysis most likely indicates the effect of targeting tight glycemic control in selected patients in many ICUs in diverse settings using different treatment regimens, different methods of blood glucose monitoring, and variable levels of quality control. This may be much closer to the effect observed when tight glycemic control is adopted in everyday clinical practice than the results observed in the initial study by van den Berghe et al.<sup>1</sup>

How might the results of the NICE SUGAR study influence a future meta-analysis? Blood glucose management in the NICE SUGAR study is standardized across the 42 sites by the use of a Web-based treatment algorithm that captures blood glucose measurements in real time. Although comprehensive data on glycemic control will be available, concerns over the accuracy of bedside blood glucose measurement will remain; thus further effectiveness data will be available for future meta-analyses. If the study reports a reduction in mortality with tight glycemic control, it will likely be enough to push tight glycemic control over the line and make calls for tight glycemic control to be a standard of care irresistible. If the result is neutral or adds evidence against the use of tight glycemic control, should interest in tight glycemic control in critically ill adults be abandoned? As patients in the higher range (control) group in NICE SUGAR have their blood glucose controlled to a target of less than 180 mg/dL, even a negative study will not provide evidence in favor of abandoning glucose control. However, those investigating tight glycemic control should take a step back and address the fundamental questions of defining quality standards for tight glycemic control, finding affordable methods of frequent and highly accurate measurement of blood glucose in the ICU, and conduct multicenter efficacy studies to determine if tighter glycemic control can reduce mortality under optimal conditions.

If tighter glycemic control (80-110 mg/dL) can be proven effective in optimal conditions, determining how to make that benefit available to millions of critically ill patients in both developed and resource-poor countries around the world would be a truly worthwhile challenge. There is no simple or clear answer to the complex problem of glycemic control in critically ill adults; at present, targeting tight glycemic control cannot be said to be either right or wrong.

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**Dedication:** This editorial is dedicated to the memory of our friend and colleague Dr Naresh Ramakrishnan (1968-2008) who died July 1, 2008.

**Disclaimer:** Dr Finfer is the chief investigator and chairs the international management committee for the NICE SUGAR study. Dr Finfer had no knowledge of outcome data from the NICE SUGAR study when writing this editorial.

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