

# Differences in outcome between the NICE-SUGAR and Leuven trials: biological mechanisms of intensive glucose control in critically ill patients

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Life is an error-making and an error-correcting process, and nature in marking man's papers will grade him for wisdom as measured both by survival and by the quality of life of those who survive.

Jonas Salk (1938)

The physiological response to stress is the basis of survival of the species. Crudely termed "fight or flight", activation of sympathoadrenal mechanisms prepares the host to mount an intrinsic defence against, or removal from, a threat. Translating this teleological process to the critically ill patient is, on the one hand, appropriate when describing the complex innate and adaptive responses to "fight" acute illness and injury, but on the other hand, inappropriate because of the patient's inability to "fly".

In the past decade, a number of clinical trials have challenged the way clinicians have interpreted basic science research and translated neurohumoral and endocrine therapies into practice.

Foremost of these was the landmark Leuven study of intensive insulin therapy in 2001, which demonstrated a 32% adjusted relative reduction in intensive care unit mortality in surgical intensive care patients through maintaining blood glucose concentration in the range 4.4–6.1 mmol/L (intensive insulin therapy) compared with 10.0–11.1 mmol/L (conventional insulin therapy).<sup>1</sup> This remarkable reduction in mortality was attributed to a "reduction in multiple organ failure with a septic focus, documented on postmortem examination". Intensive therapy was considered to have substantially more benefit in the subgroup of patients with prolonged critical illness (>5 days), with an absolute reduction of 9.6% in ICU mortality and significant reduction in morbidity.

A second Leuven study, in medical intensive care patients in 2006, failed to find a reduction in hospital mortality or morbidity in the intention-to-treat population, although a significant reduction in mortality and morbidity was demonstrated in a post-hoc analysis of the subgroup of patients who stayed in the ICU for longer than 3 days.<sup>2</sup>

When the data from these two studies were pooled, the use of intensive insulin therapy was associated with a 3.2% absolute reduction in hospital mortality in all patients and a

7.8% absolute reduction in long-stay patients.<sup>3</sup> The median dose of insulin in the intensive insulin therapy group was 59 units/day (interquartile range [IQR], 37–84 units/day) compared with 1 unit/day (IQR, 0–24 units/day) in the conventional insulin therapy group. The incidence of hypoglycaemia was 11.8% compared with 1.5% in the conventional group.

Questions about the applicability of the single-centre Leuven studies remained — particularly the emphasis on post-hoc subgroup analyses, high incidence of hypoglycaemia, complexity of the intervention and concerns about the generalisability of the results because of the unconventional use of high concentrations of intravenous glucose in parallel with the administration of insulin.

Some of these questions were addressed by the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation — Survival Using Glucose Algorithm Regulation) Study.<sup>4</sup> This international, randomised controlled trial of 6104 medical and surgical patients demonstrated that intensive insulin therapy increased the absolute risk of death at 90 days by 2.6%. The increase in mortality developed beyond 28 days, and there was no difference in the development or resolution of organ failure(s) and other indices of morbidity. Most deaths were due to cardiovascular causes, predominantly distributive shock. Patients receiving intensive insulin therapy received higher doses of corticosteroids, predominantly for the treatment of septic shock. Patients in the intensive group also received significantly more insulin than the conventional group (50.2±38.1 v 16.9±29 units/day). The incidence of hypoglycaemia was 6.8% in patients receiving intensive insulin therapy, compared with 0.5% in those receiving conventional therapy.

These results are completely at variance with those of the Leuven trials and subsequent smaller studies, which found no differences in mortality.<sup>5,6</sup> This may be explained in large part by the methodological superiority of the NICE-SUGAR Study in terms of statistical power and internal and external validity, as discussed by Henderson and Finfer in this issue of the *Journal* (page 175),<sup>7</sup> However, what is striking is the development of late mortality and higher incidence of corticosteroid-dependent ("vasoplegic") distributive shock in the NICE-SUGAR Study. In comparing the Leuven trials and NICE-SUGAR Study, key differences emerge that sug-

See also Henderson and Finfer, page 175

gest biological mechanisms that may have been responsible for the different outcomes, independently of the substantive methodological differences.

The Leuven studies posed the initial question whether the benefit of intensive insulin therapy arose from attenuation of the toxic effects of hyperglycaemia or from the benefits of augmenting insulin levels. Direct cellular glucose toxicity has been attributed to downregulation of adrenergically mediated glucose transporters, particularly those in hepatocytes and pancreatic  $\beta$ -cells, and upregulation of endothelial and neural cells by proinflammatory cytokines, resulting in overloading of cellular glucose.<sup>8</sup> Indirectly, excessive oxidative phosphorylation has been implicated in apoptosis through the production of cytokine-mediated mitochondrial damage.<sup>9</sup> Insulin resistance is an endogenous response that facilitates cellular uptake of glucose under conditions of stress. This may be due to activation of counter-regulatory mechanisms, specifically catecholamine-, cortisol- or cytokine-mediated attenuation of insulin-receptor signalling.<sup>10</sup> Given that all patients in the Leuven studies received excessive calories (15 kcal/kg/day [63 kJ/kg/day], of which 80% was administered parenterally),<sup>3</sup> they may have developed a subclinical state of relative "glycaemic stress", particularly in the conventional insulin therapy group, which had higher mortality than the intensive insulin therapy group. This differs markedly from the NICE-SUGAR Study, where patients received about 11 kcal/kg/day (46 kJ/kg/day), of which 71.2% was administered enterally. In the context of a large-scale pragmatic trial, this does not represent a state of relative "starvation", but the reality of delivering the intervention at the bedside.

Augmentation of insulin levels, either endogenously or by exogenous administration, has been associated with cellular expression of anti-apoptotic effects. Some limited benefit in preserving myocardial function has been demonstrated in patients undergoing cardiopulmonary bypass.<sup>11</sup> Whether insulin provides a prima-facie benefit in the absence of relative hyperglycaemia is unknown. As a principal anabolic hormone, insulin excess under conditions of an extended stress response may represent a state of "teleological antagonism", primarily prolonged sympathoadrenal activation with associated downregulation and desensitisation of adrenergic-receptor populations. The use of corticosteroids has evolved as a catecholamine-sparing strategy to limit the dose of exogenous vasopressors in patients with exhausted endogenous responses.<sup>12</sup> The association between neurohormonal decompensation and increased cardiovascular deaths in a non-diabetic population of critically ill patients receiving high doses of insulin remains highly speculative and needs further elucidation to demonstrate causality.

Identifying biological mechanisms of interventions that produce harm or benefit is fundamental to understanding critical illness. However, these remain difficult to demonstrate in clinical trials of heterogeneous populations. Ensuring high-quality research methods and determining effects on robust patient-centred outcomes remain the standard by which interventions are judged. In this regard, the NICE-SUGAR Study provides compelling evidence that intensive insulin therapy cannot be recommended in critically ill patients.

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