Commentary

NICE-SUGAR: the end of a sweet dream?

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Abstract

The results of the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation) trial were released last March. The primary outcome variable, 90-day mortality, was actually increased in patients randomly assigned to intensive insulin therapy, as compared with an intermediate target range for blood glucose. These findings, reflecting data collected in a set of more than 6,000 patients, clearly refute the external validity of tight glucose control. Future research will probably focus on several questions raised by the divergent results reported from investigations in the field of glucose control in the critically ill.

On Tuesday, 24 March 2009 at 10:05 hours, the Erasmus Room of the Exhibition and Congress Centre of Brussels was overcrowded. Attendees from all over the world had gathered for a well planned and widely announced event. Professor Simon Finfer, from the Royal North Shore Hospital of Sydney, Australia was about to release the results of the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation) trial, the largest clinical study conducted in critical care medicine to date. At the end of his presentation, the article was published and available on the website of the *New England Journal of Medicine* [1].

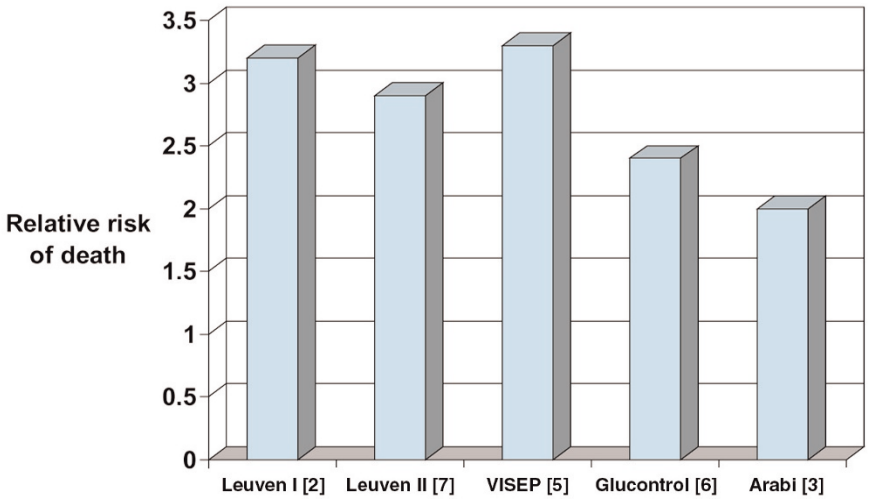
NICE-SUGAR was designed to test whether tight glucose control by intensive insulin therapy (TGCIIT; $n = 3,010$ evaluable patients) increases 90-day survival as compared with less strict glucose control ($n = 3,012$ evaluable patients). The issue of TGCIIT has been among the most popular and passionate areas of debate and discussion since 2001, when the landmark Leuven I study [2] was published. Several investigators [3-6] and the Leuven medical ICU team [7] had already assessed the effects of TGCIIT in various settings and conditions. These trials failed to reproduce the impressive improvement in survival reported in the Leuven I study [2]. It is unsurprising (in view of the now presented NICE-SUGAR findings) that two recent meta-analyses [8,9] concluded simply that tight glucose control is not associated with significantly reduced hospital mortality. Criticisms of each of the individual studies were raised, including inadequate statistical power and the use of various degrees of glucose control, all lower in the subsequent trials [3-7] than in the initial Leuven I study [2]. Therefore, the NICE-SUGAR trial was eagerly awaited by the intensive care medicine community worldwide.

The sample size of NICE-SUGAR was calculated to detect a 3.8% absolute difference in mortality (treatment effect reported in the Leuven I trial) with a power of 90%, assuming a baseline mortality of 30% [2]. NICE-SUGAR was conducted in a network of intensive care units that had previously collaborated and included patients in large-scale trials. A web-based electronic algorithm was used to adapt the insulin infusion rate. Under these conditions (optimal for successful performance of a multicentre trial) the primary outcome variable, namely 90-day mortality, was found to be increased from 24.9% in the conventional/control group arm to 27.5% in the intensive treatment arm, which is in complete contrast to the findings of the Leuven I trial. These findings allow us to address certain issues and provide some answers, but they also raise new questions.

The main issue considered by NICE-SUGAR - whether the Leuven I trial has external validity - is clearly addressed in the negative, in contrast to previous hopes and beliefs. Possible reasons for the lack of external validity are multiple and include major differences in the amount of intravenous glucose infused, the frequency of use of enteral nutrition and possibly a lower 'commitment' to TGCIIT by centres other than Leuven. Nonetheless, NICE-SUGAR probably succeeded in separating the levels of glycaemia reached in the two experimental groups, even though the interquartile ranges of the values are not stated in the report [2]. Whatever the reason for the disparity between the results of the Leuven I

NICE-SUGAR = Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation; TGCIIT = tight glucose control by intensive insulin therapy.

Figure 1



Relative risk for death in patients with hypoglycaemia. Shown are the relative mortality rates in patients included in prospective studies of tight glucose control by intensive insulin therapy who experienced hypoglycaemia versus those who did not. Mortality rate was increased by a factor of 2 to 3.3 among patients who experienced hypoglycaemia.

trial and other studies, some standards of care will be changed. The Endocrine Society has already issued a statement [10], just after the publication of the results of NICE-SUGAR, advocating the need for more nuanced recommendations on glucose control. Likewise, other official bodies (for instance, the Joint Commission on Accreditation of Healthcare Organizations, the Institute for Healthcare Improvement and the Volunteer Hospital Organization) that issued recommendations on tight glucose control in critically ill patients will need to re-consider their position.

The new questions raised by NICE-SUGAR probably include the actual validity of the concept of 80 to 110 mg/dl (4.4 to 6.1 mmol/l) as 'normoglycaemia' or even desirable glycaemia during critical illness [11]. Another key but unresolved and poorly investigated issue is the possible nonglycaemic effects of insulin in the late divergence in the cumulative survival curves observed both in the Leuven studies [2,7] and in NICE-SUGAR [1], albeit in opposite directions. Other pending questions raised include the risks and potentially harmful effects of high variability in glucose levels, which are probably influenced by TGCIIT [12-14]. Finally, the absence of risks for hypoglycaemia, although not studied specifically in NICE-SUGAR, is questionable when the mortality rate of patients who experienced hypoglycaemia was systematically two to three times higher than in nonhypoglycaemic patients (Figure 1). The effects of hypoglycaemia can be particularly harmful in brain-injured patients [15,16].

With these uncertainties in mind, the only target for blood glucose that can currently be recommended will probably be in the intermediate range, even in the absence of direct evidence. An intermediate level will probably allow safer although effective glucose control [17].

Competing interests

The author declares that they have no competing interests.

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