Tight glucose control in the post-NICE SUGAR era

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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 of the study, 90-day mortality, was found increased in patients randomised to intensive insulin therapy, as compared with insulin therapy that targeted an intermediate range for blood glucose. These findings reported from data collected in a set of more than 6,000 patients invalidate the external validity of tight glucose control and attenuates the wave of enthusiasm that followed the release of the Leuven I study in 2001. Future research will be needed to address the numerous questions raised by the divergent results reported from investigations in the field of glucose control in the critically ill.

Keywords - stress metabolism, stress hyperglycaemia, intensive insulin therapy, carbohydrate metabolism, hypoglycaemia.

During the 2009 edition of the International Symposium of Intensive Care and Emergency Medicine in Brussels, attendees from all over the world gathered there for a very 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. Exactly at the end of his presentation, the article was published and available on the site of the New England Journal of Medicine [1].

NICE-SUGAR was designed to test whether tight glucose control by intensive insulin therapy (TGCIIT targeting a blood glucose between 80 and 110 mg/dl, n=3,012 evaluable patients) increased the 90-day survival, as compared to a less strict glucose control (n= 3,012 evaluable patients, blood glucose target below 180 mg/dl). The issue of TGCIIT has been one of the most popular and passionate areas of debate and discussions from 2001, on the year of publication of the landmark Leuven I study [2]. Several investigators [3-6], and the Leuven team of the medical ICU [7] already assessed the effects of TGCIIT in different settings and conditions. These trials failed to reproduce the impressive improvement in survival reported from the Leuven I study [2]. Not surprisingly, two recent meta-analyses [8, 9] concluded simply that tight glucose control is not associated with a significant reduction in hospital mortality. Criticisms of each of the individual studies were expressed, including a too low statistical power and various degrees of glucose control, being lower in the subsequent trials [3-7] than in the Leuven I study [2]. Therefore, the NICE-SUGAR trial was eagerly awaited by the community of intensive care medicine 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 [2]) with a power of 90%, assuming a baseline mortality of 30% [2]. NICE-SUGAR was performed in a network of ICUs used to include patients in large-scale trials. A web-based electronic algorithm was used to adapt the insulin infusion rate. In these optimal conditions for the successful performance of a multicentre trial, the primary outcome variable, 90-day mortality, was found increased from 24.9 % in the conventional/control group arm to 27.5 % in the TGCIIT, in complete contradiction with the findings of the Leuven I trial. In fact, these results allow to address and to provide an answer to some issues, but actually also raise more new research questions.

First, the answer to the question of the external validity of the Leuven I trial is clearly negative, in contrast to previous hopes and beliefs. Possible reasons for the lack of external validity are multiple, including major differences in the amount of intravenous glucose infused, the frequency of use of enteral nutrition and possibly a lower “commitment” to TGCIIT by other centers than Leuven. Nonetheless, the 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 publication [2]. Whichever the reason of the disparities between the results of the Leuven I trial and the other studies, some standards of care will be changed. The Endocrine Society already issued a statement just after the publication of the results of NICE-SUGAR [10] which advocates the need for more nuanced recommendations for glucose control. Likewise, other official bodies (e.g. Joint Commission on Accreditation of Healthcare Organization, the Institute for Healthcare Improvement and the Volunteer Hospital Organization), who issued recommendations for tight glucose control in critically ill patients will need to re-consider their position.

Second, the new questions raised probably include the actual validity of the concept of 80-110 mg/dl as “normoglycaemia”, or even desirable glycaemia during critical illness [11]. Another key but yet unresolved and poorly investigated issue is the
possible nonglycaemic effects of insulin in the late-occurring difference in the cumulative survival curves observed both in the Leuven studies [2, 7] and in NICE SUGAR [1], albeit in opposite directions. The other pending questions comprise also the risks and potentially harmful effects of high glucose variability, which is likely influenced by TGCIIT [12, 13, 14]. Finally, the absence of risks of hypoglycaemia, although not studied specifically in NICE-SUGAR is questionable when the mortality rate of patients who experienced hypoglycaemia recorded in the other prospective studies was systematically two to three times higher than in non-hypoglycaemic patients [2-6, 15]. The effects of hypoglycaemia can be particularly harmful in brain-injured patients [16, 17].

Having these uncertainties in mind, the currently recommendable target for blood glucose will probably be in the intermediate range, even in the absence of direct evidence. An intermediate level will probably allow a safe and effective glucose control [18].

References


