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Intensive insulin therapy to maintain normoglycemia after cardiac surgery

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ABSTRACT

Drugs used in the perioperative period could have an effect on survival as recently pointed out by an international consensus conference on the reduction in mortality in cardiac anesthesia and intensive care. Insulin infusion to achieve a strict glycemic control is the best example of how an ancillary (i.e. non-surgical) drug/technique/strategy might influence survival rates in patients undergoing cardiac surgery. The author of this "expert opinion" presents her insights into the use of insulin in this setting and suggest that based on available evidence based medicine, insulin infusion, titrated to "normoglycemia" is a complex intervention, that not only requires the simple administration of a "drug", the hormone insulin, but also needs tools and skills to accurately measure and control blood glucose to achieve normoglycemia while avoiding hypoglycemia and large glucose fluctuations.

Keywords: *insuline, anesthesia, cardiac surgery, intensive care, mortality*

Dr. Landoni and colleagues are to be congratulated for their efforts to assess the existing evidence on all ancillary drugs/techniques/strategies that could potentially improve survival rates of patients undergoing cardiac surgery, and to draft a list of those that merit urgent further investigation (1, 2). This list was the result of an International Consensus Conference that met last summer.

The activities of this group to review the literature on these interventions and to weigh their potential impact using evidence-based methodology are vital to efficiently endorse effective strategies by practicing clinicians, and to systematically improve patient care It will be interesting and important to see the results from further investigations as well as reports from the implementation process of these treatments into clinical practice.

Listed top, and annotated with the highest level of agreement, appears insulin infusion titrated to maintain normoglycemia in adult patients admitted to intensive care after cardiac surgery.

This intervention has shown, in a large randomized controlled study (RCT) of adult intensive care unit (ICU) patients, among which 60 % after cardiac surgery, to increase survival rate and to reduce morbidity. The publication of that study in 2001 (3) was followed by another RCT performed in

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infants and children, among which again 75 % were patients after cardiac surgery, which confirmed the benefits (4). Also in implementation studies, the strategy has shown to generate outcome benefits in the cardiac surgery population (5, 6).

The intervention that was investigated comprises insulin infusion, which is titrated to "normoglycemia". It is thus a complex intervention, that not only requires the simple administration of a "drug", the hormone insulin, but also needs tools and skills to accurately measure and control blood glucose to achieve normoglycemia while avoiding hypoglycemia and large glucose fluctuations. All of the aspects of the "package" are equally important.

The concept of infusing the hormone insulin in order to improve outcome of cardiac surgery patients was not new. It was launched almost 5 decades ago by Dr. Sodi-Pallares, who advocated the infusion of insulin together with glucose and potassium (GIK) with the intention to provide the ischemic heart with an alternative metabolic substrate that requires less oxygen than fatty acids, and to prevent arrhythmia (7).

However, the intervention to titrate insulin to normoglycemia in patients with critical illness was investigated for a different reason, namely to avoid complications that occur because of toxic effects of hyperglycemia during stress or illness. Indeed, it has been shown in many large scale observational studies that there is a clear J-shaped association between adverse outcomes and blood glucose levels in all types of patients suffering from acute critical illnesses (8, 9). This applies to the admission blood glucose values but also to the average blood glucose values during intensive care.

The lowest risk is associated with "age-adjusted normoglycemia", especially in patients without a history of diabetes mellitus. In patients with long-standing diabetes mellitus, this curve is flattened and somewhat shifted to the right, so slightly higher blood glucose levels could be associated with the lowest risk for diabetic as compared with non-diabetic patients (9). Such an association could either suggest that hyperglycemia, any level higher than "normoglycemia", is an adaptive response to illness, proportionately to the illness severity, or else that it contributes to adverse outcome as is the case in diabetes mellitus. In the RCT published in 2001, the hypothesis was the latter: namely that toxic effects of hyperglycemia occur during stress and illness (3, 10). Hence, in the intervention group of this study of patients admitted to ICU, targeting strict normoglycemia (80-110 mg/dl) with a continuous insulin infusion was compared with tolerating hyperglycemia up to 215 mg/dl in the control group. Sixty percent of the patients had been admitted to intensive care after complex or complicated cardiac surgery with high euroscores (3, 11).

This study found that titrating insulin infusion to prevent blood glucose exceeding the upper normal limit, starting immediately after surgery and continuing throughout the entire stay in ICU, substantially reduced morbidity and mortality, a benefit that was maintained at least up to 4 years after surgery (11). Subsequently, a similar study was performed in critically ill infants and children, of which 75 % was admitted to ICU after surgery for complex congenital cardiac anomalies (4).

Titrating insulin to a blood glucose level that is equal to the age-normal fasting blood glucose level generated similar outcome benefits as in the adult population, with a striking protection of the heart, fewer infections, shortened ICU stay and a reduced mortality. Studies that documented implementation of a blood glucose lowering intervention to achieve normoglycemia in patients after lower risk cardiac surgery also confirmed the benefits (6, 12). In depth

analyses of the results suggested that the prevention of hyperglycemia, not the infusion of insulin per se, explained most of these benefits (13, 14). Studies in animal models of critical illness and in cell culture models further unraveled this important aspect of glucose toxicity, and pointed to direct damaging effects of hyperglycemia on cell integrity in liver, kidney, the endothelium, immune cells and the heart (15-21).

A damaging effect on the mitochondria appears to play a crucial role in the adverse effects of hyperglycemia (16, 17) and anti-inflammatory effects could be involved as well (22). Further post-hoc analyses of the available data from the RCTs suggested a dose response (13, 14): most effect on morbidity and on mortality was obtained when true normoglycemia was achieved. But to reduce mortality, 75 % of the benefit may already have been present when blood glucose levels were effectively lowered to below 150 mg/dl. It remains hitherto unclear, however, from which level of blood glucose onward the toxic effects of hyperglycemia become clinically important, as RCTs addressing this question have not been performed.

The largest RCT to date on the topic of blood glucose control in ICU patients is the NICE-SUGAR trial, that investigated 6100 patients in 42 centers predominantly in Australia, New Zealand and Canada (23). Although this trial was meant to be a "multi-center repeat study" of the Leuven trials, it was not a "repeat study" as it studied a different intervention in a different patient population using different targets and tools for blood glucose control.

First, the population did not include patients after cardiac surgery. Second, it compared targeting strict normoglycemia with an intermediate target for blood glucose control (achieving mean blood glucose levels of around 150 mg/dl) instead of tolerating hyperglycemia to 215 mg/dl. Third, the tools used to measure blood glucose levels (different types of hand-held meters) were highly inaccurate and therefore not suitable to target such a narrow range for blood glucose (24). Fourth, the algorithm that was used did not allow stable control of the true blood glucose levels and resulted in a broad overlap between the measured blood glucose levels in both study arms (25). Finally, the patients did not receive early parenteral nutrition to complete insufficient enteral nutrition, in contrast to the patients in the Leuven trials.

NICE-SUGAR suggested that, with the tools and methods used, targeting an intermediate level of blood glucose is safer than attempting to reach strict normoglycemia.

This is the correct conclusion from that trial, but all the above listed methodological differences make it difficult, if not impossible, to directly compare this trial with the proof-of-concept Leuven trials. Since cardiac surgery patients were not included, also the relevance for this patient population remains unclear. In addition, the outcome of NICE-SUGAR underlines the importance of applying all aspects of a complex intervention when moving from a proof-of-concept study to a "repeat study" or when implementing the intervention in clinical practice (26).

So where do we go from here? Based on high level evidence, insulin infusion titrated to normoglycemia in ICU after cardiac surgery is ranked at the top of the list of "ancillary drugs/techniques/strategies that could potentially improve survival rates of patients undergoing cardiac surgery" by the International Consensus Committee (1, 2).

What should be done next before we can safely advise to implement the intervention in routine clinical practice?

In order to prove generalizability of the findings from the Leuven studies, a large, multi-center "repeat" RCT is required in the cardiac surgery patient population.

This implies that the study should include cardiac surgery patients only and should investigate the full package of the intervention with all the details described above being copied.

The intervention, titration insulin to achieve normoglycemia, should be compared against "tolerating hyperglycemia", not against an intermediate target, as the latter will inevitably result in too broad overlap and thus insufficient separation of blood glucose levels in the groups to study an outcome difference.

Also, the study should be large enough to have enough statistical power. In view of the variable mortality rates for patients undergoing cardiac surgery, which can be as low as < 3 % for isolated coronary bypass surgery up to 11 % for complicated or combined valvular surgery (27-29), depending on the case-mix and types of surgery of the patients in the study, this could mean that a mega-trial is needed, with sample sizes that may range from 6.000 to 26.000 patients.

In addition, if due to change in clinical practice, the control group would have an intermediate blood glucose target, even smaller benefits can be hypothesized and the number of patients required will further rise exponentially. In view of these complicating issues, it is highly unlikely that such a large trial will be performed in the very near future.

In the absence of such results from generalizability studies, centers may consider the current evidence strong enough to implement the intervention in clinical practice. In that case, the clinical teams should be willing to implement all aspects of the "package".

This requires frequent blood glucose monitoring with accurate measurement tools by trained staff and nurses, validated guidelines for insulin treatment adjustment using accurate equipment for insulin administration, and all the educational steps that are required before embarking on such a complex intervention.

It can be done, as shown elegantly by the report from a study on the transition to strict blood glucose control in a prestigious cardiac surgery center in Aalst, Belgium (5, 6). But, in view of the complexity of the intervention, it will probably require the development of new accurate continuous sensors for blood glucose monitoring, ideally in combination with a closed-loop algorithm, before it will be adopted widely. Such systems do not exist at this moment, although several companies are working on this development.

Finally, it is the responsibility of the ICU teams to carefully document any impact on outcome of implementation of a novel intervention in clinical practice, in order to guarantee patient safety.

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