GLYCEMIC CONTROL IN PERIOPERATIVE PERIOD AND ICU – AN UPDATE

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The three Leuwen studies (1-3), especially the first one published in 2001 (1), caused a revolution in the approach to glucose control in the intensive care medicine. Tight glucose control with intensive insulin therapy aiming for normoglycemic range (4.4–6.1 mmol/l or 80–110 mg/dl) compared with a usual care at that time, i.e. tolerating hyperglycemia as an adaptive response and thus starting insulin only when blood glucose levels exceeded the renal threshold (12 mmol/l or 215 mg/dl), significantly lowered both mortality and morbidity in adult surgical ICU patients. Their ICU mortality decreased by 42% (from 8.0 to 4.6%, i.e. absolute risk reduction 3.4%) while in-hospital mortality was reduced by 34% (from 10.9 to 7.2%, i.e. absolute risk reduction, 3.7%). Their morbidity also decreased due to prevention of organ failure evidenced by a reduction of duration of mechanical ventilation, by a decrease in the incidence of acute kidney failure requiring dialysis or hemofiltration by 41% and of polyneuropathy by 44% and by preventing severe infections by 46%. These impressive findings were explained by prevention of glucose toxicity to vital cells.

Due to these results achieved by such a simple and cheap intervention as an insulin infusion, professional societies soon issued new guidelines on glucose management and regulatory authorities adopted tight glucose control as a standard care and as a measure of a quality of care although they were aware of additional labor and financial costs due to necessary regular and frequent glucose checks.

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However, subsequent large trials such as VISEP (4) (Volume substitution and Insulin therapy in severe SEPsis, n=537 patients with sepsis and/or septic shock), Glucontrol (5) (n=1101 mixed critically ill patients) and Nice-Sugar (6) (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation, n=6104 patients expected to require treatment in the ICU longer than 3 days) failed to confirm the expected benefit of tight glucose control. Surprisingly, all of these trials resulted in increased mortality in intervention arms and higher incidence of hypoglycemic episodes. VISEP and Glucontrol trials had even to be stopped prematurely.

What are the causes for this discrepancy? They are many. Besides logistical problems such as different routes for insulin administration and types of insulin infusion pumps, different sampling sites (arterial, venous, capillary) and different types of instrument for blood glucose measurement (various glucometers, point-of-care analyzers or laboratory measurement) as well as different nutritional strategies and varying levels of expertise with the therapy among the intensive care nurses I would like to emphasize here four reasons.

First, there is a substantial difference in the target ranges for blood glucose in the control groups of these trials, 10-11.1 mmol/l = 180-200 mg/dl in VISEP (4) or 7.8-10 mmol/l = 140-180 mg/dl in Glucontrol (5) and Nice-Sugar (6) compared to > 12 mmol/l or 215 mg/dl in the first Leuwen study (1). Control patients in these newer studies could thus already have some benefit from lower glycemia.

Second, there is a difference in patients´ populations. It is easier and quicker to correct blood glucose levels in surgical patients, in which hyperglycemia is acutely triggered by the stress of surgery or trauma, than in medical patients, in which hyperglycemia can be present for longer time periods and thus adaptive changes for protection against hyperglycemia may already have been induced and acute lowering of blood glucose may not be beneficial. Alternatively, the time window for prevention of toxicity may have passed and irreversible damage may have been done (7).

Third, intensive insulin therapy is associated with frequent hypoglycemic episodes (≤ 2,2 mmol/l in 6.8% (6), 8.7%(5) to 17%(4) or even to 25% in the pediatric Leuwen 3 study (3) of patients in intervention groups compared to only 0.05% [39/765] in the intervention group of Leuwen 1 study)(1) which activate sympathetic nervous system. Apart from sympathetic hyperactivity induced by hypoglycemia, insulin also shifts potassium into the cells (this effect is frequently used for therapy of hyperkalemia) and thus leads to hypokalemia which can provoke arrhythmias. Indeed, in Nice-Sugar trial the excess of deaths (78, i.e. 829/3010 in the intervention arm

vs. 751/3012 in the control arm) was attributed to cardiovascular causes. This is consistent with results of intensive glucose control trials in chronic diabetic patients such as ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease Preterax and Diamicron Modified Release Controlled Evaluation) and VADT (Veterans Administration Diabetes Trial) which failed to show that intensive glucose control aiming for a glycated hemoglobin HbA1c level < 7% significantly reduces cardiovascular events. The ACCORD trial even suggested that - under certain circumstances - intensive glucose control is associated with an increased risk for cardiovascular and all-cause mortality (8). Although the exact mechanisms responsible for an increase in mortality in the ACCORD trial are still not known, there was an association between increased rates of mortality with higher rates of severe hypoglycemia in the intensive glucose control group (9).

Finally, insulin acts not only on glucose lowering its level in blood but equally important are its effects on fat (promotes fat storage in adipose tissue) and protein metabolism (inhibitory effect on proteolysis). Insulin infusion, especially in high doses (≥ 0.05 units/kg/hour) inhibits hormone-sensitive lipase in adipose tissue and thus lowers free fatty acid levels in blood which serve as a main source of energy for the healthy heart in the fasted state (10). Although fatty acids require more oxygen than glucose for the same amount of generated adenosine triphosphate (ATP) and thus they are not very efficient source of energy in states of ischemia, some hearts strictly depend on fatty acids because they have lost their metabolic flexibility due to the disease (11). However, fatty acid levels are usually not routinely measured and known in clinical practice because their analysis is influenced by a variety of factors in the preanalytical stage. In addition, insulin also blocks the availability of ketone bodies, another important source of energy for the heart. The availability of substrates significantly impacts the tolerance of the heart against ischemia-repefusion injury and its ability for subsequent recovery (12). Taken together, excess of insulin leads to the lack of energy substrates for the heart (hypoglycemia, low levels of fatty acids and ketone bodies), which can be detrimental. Furthermore, high-dose insulin therapy also results in a significant reduction in plasma amino-acid levels, particularly branched-chain amino-acids, which become essential regulators of cardiac ATP production during myocardial ischemia and in the postischemic reperfusion period (13,14).

Blood glucose control during surgery seemed less important until recently. However, it came out that hyperglycemia worsens neurological and cardiac injury caused by ischemia-reperfusion, blocks cardioprotection, aggravates

renal damage, attenuates immune functions and increases the risk of infectious complications. Hypoglycemia masked by general anesthesia is similarly detrimental. Therefore, maintaining blood glucose levels in reasonable ranges seems nowadays equally imperative as in the ICU. Moreover, not only hyperglycemia and hypoglycemia are dangerous, even glucose variability is associated with worse outcomes (15). That´s why adequate preoperative management is also essential. Diabetic patients or patients at risk for postoperative hyperglycemia should have their long-term compensation checked by measuring the HbA1c levels before operation. Some authors suggest delaying the surgery, if possible, until the glucose control can be optimized (16). Intraoperative and postoperative blood glucose levels should be maintained below 10-11.1 mmol/l or 180-200 mg/dl and blood glucose levels monitored every 30-60 minutes or even more frequently in cardiac surgery with rapidly changing insulin sensitivity due to cardioplegia, cooling or rewarming (16). Intraoperatively, glucose non-containing solutions are usually infused to avoid postoperative hyperglycemia. However, a continuous glucose infusion in a low dose can prevent surgery-induced muscle protein breakdown and activate insulin signaling. Schricker et al. thus suggest to administer 2 mg glucose/kg/min.(17) Insulin resistance can also be improved by preoperative carbohydrate treatment (18).

In summary, maintaining normoglycemia during the perioperative period and ICU stay has the potential to prevent secondary injury to threatened vital organ systems and thereby to improve outcome of critically ill patients. However, there is also a risk associated, and thus the optimum level as well as the optimal mode to reach that level should be defined (7). Nowadays, it is proved that optimal blood glucose range is less than 10 mmol/l or 180 mg/dl or maybe lower as suggested by the J-shape curve of statistical asociation between mortality and blood glucose levels in which the nadir, i.e. the lowest risk of death, lies between 5-7 mmol/l = 90-126 mg/dL (19). The best advice is therefore to individualize glucose control based on the patient's characteristics, comorbidities, procedural duration, location, and the potential impact of hypoglycemia or hyperglycemia on outcome (20).

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