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Glucose control in critically ill patients in 2009: no alarms and no surprises

Controle glicêmico em terapia intensiva 2009: sem sustos e sem surpresas

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ABSTRACT

Glucose control is a major issue in critical care since landmark publications from the last decade leading to widespread use of strict glucose control in the clinical practice. Subsequent trials showed discordant results that lead to several questions and concerns about benefits and risks of implementing an intensive glucose control protocol. In the midst of all recent controversy, we propose that a new glycemic target -150mg/dl) should be aimed. This target glucose level could offer protection against the deleterious effects of hyperglycemia and at the same time keep patient's safety avoiding hypoglicemia. The article presents a critical review of the current literature on intensive insulin therapy in critically ill patients.

Keywords: Blood glucose; Hypoglicemia/prevention & control; Insulin, Sepsis/prevention & control; Critical care

INTRODUCTION

In the last decade a number of studies have been published on glucose control in the intensive care setting. A better understanding of the impact of hyperglycemia was provided by studies on the physiopathology basis of cellular glucotoxicity[1] as well as by epidemiological studies that revealed a strong association between hyperglycemia and intensive care unit (ICU) mortality. Therefore, establishing an efficient and safe glucose control strategy has become the most likely focus of recent clinical trials.

This idea is in accordance with current conceptual framework in critical care, where it is usually inferred that the normalization of physiological variables is to be directly associated with clinical benefits.[2] However, this line of thinking is reductionist and tends to oversimplify and neglect several of the complex pathophysiological interactions that are present in an acute severe illness. Thus it is often disappointing to the critical care scientific community when faced with conflicting results obtained from negative clinical trials. Therefore, considering the limitation of the reasoning behind current clinical trials it is not surprising that so many have failed in translating "sound pathophysiological data" into "effective clinical interventions".[3]

Almost eight years after the publication of the landmark study by van den Berghe et al.,[4] glucose control has become fashionable and a standard of care for ICU patients. However, recent meta-analysis has shown discordant results.[5] Therefore, the actual challenge is to achieve an op-

timal strategy, defining how intensive glucose control should be, without putting patient's safety at stake and especially assessing subpopulations of critically ill patients that might benefit from this approach.

Results from clinical studies: benefits, risks and current targets

Hyperglycemia has already been demonstrated as a marker of poor prognosis in medical and surgical critically ill patients.[6] In patients with acute ischemic stroke who received recombinant plasminogen activator treatment, the odds for neurologic improvement decreased as admission glucose level increased (OR: 0.76 per 100mg/dL admission glucose CI: 0.61-0.95), among other deleterious effects.[7] In a post-hoc analysis of DIGAMI 1 trial (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) with acute myocardial infarct (AMI) patients, blood glucose at admission was one of the predictors of poor prognosis (OR 1.08 IC: 1.04-1.12).[8] More recently, Ceriello et al. also evaluated patients with AMI, with diabetes mellitus previously diagnosed or not, showing that hyperglycemia increases mortality by up to four times after the cardiovascular event, as the chances of developing heart failure and cardiogenic collapse.[9] However, it was unclear if hyperglycemia was the cause of increased mortality and adverse effects or just an epiphenomenon of critical illness.

To test the hypotheses that hyperglycemia had a causal role in adverse events and that glucose control was able to reduce the odds of poor prognosis in hyperglycemic, critically ill patients, several trials were conducted. In the DIGAMI 1 trial, AMI patients who were randomized to intensive insulin therapy as compared to conventional treatment had reduced mortality (19: x 26% p< 0.05). The treatment effect was more pronounced in those with no history of prior insulin therapy and low cardiovascular risk. These results encouraged trials with critically ill patients.

Subsequently, in the classic Leuven study, the benefits of strict glucose control were demonstrated in surgical critically ill patients,[4] with decreased rate of organ dysfunctions and mortality when glycemia was maintained between 80-110mg/dl vs 180-200mg/dL. The benefits of intensive glycemic control seemed to be related not only to reduced glucose levels but also to the anti-inflammatory effects of insulin, decreased generation of free radicals that contribute to direct glucotoxicity and protection of mitochondrial metabolism and its ultrastructure.[1]

The result of this large single randomized controlled trial (RCT) had an enormous impact in the critical care community, with the majority of ICUs trying to implement strict glucose control by continuous insulin infusion. Main critical care organizations worldwide recommended strict glucose control as part of the standard therapy for septic ICU patients.[10] Meanwhile, van den Berghe et al., evaluated the intensive insulin therapy in a medical ICU population. Although the incidence and severity of new organ dysfunction were lower in the group with a strict control, mortality benefits were restricted to those patients with an ICU length of stay of more than three days.[11]

However, despite proven benefits of insulin use to achieve physiologic levels of blood glucose, there is a subtle limit between offering patients a protective care with intensive insulin therapy or a potentially harmful approach by increasing the risk of severe hypoglicemia. In a single center study, Clayton et al. demonstrated that high rates of hypoglycemia were present in patients with severe sepsis on strict glucose control.[12] These authors demonstrated that the more serious events were usually associated with incorrect implementation of the protocol.

In a recent RCT Brunkhorst et al. evaluated the impact of intensive insulin therapy in patients with severe sepsis.[13] The Volume Substitution and Insulin Therapy in Severe Sepsis trial (VISEP study) was stopped earlier in 2008 because of an unacceptably high incidence of hypoglycemia during the protocol implementation (17% in the intervention group x 4.1% in control group). Intensive insulin therapy was once again under attack.

Recently, more fuel was added to the glucose control controversy when the results of the NICE-SUGAR study (The Normoglycemia in Intensive Care Evaluation - Survival Using Glucose Algorithm Regulation)[14] were published. This large (n=6030) multicenter, international RCT evaluated the use of strict versus conventional glucose control in a mixed ICU population. The investigators could not show any major benefit in keeping ICU patients normoglycemic (80-108 mg / dl) as compared to maintaining their glucose levels below 180mg/dl. Moreover, there was a higher incidence of hypoglycemia in the intervention group (206 of 3016 patients – 6.8%) compared to the conventional treatment group (15 of 3014 patients – 0.5%) p<0.001. Although severe consequences related to these events were not reported,

this fact shows that intensive insulin use can increase risk of adverse events and the possibility of serious impact. However, although there were differences in the proposed glucose targets in the two treatment arms, in reality the intervention group achieved less impressive strict control (median glucose= 114mg/dl) and in the other hand the conventional therapy group achieved higher degrees of control than proposed in the study design (median glucose = 144md/dl).

Data from the Glucontrol trial (A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units), which included 1108 patients in 19 centers, was not able to find any difference in mortality between patients with strict glycemic control x conventional treatment. Again, the incidence of hypoglycemia in the intensive insulin therapy was higher (8.7% x 2.7%) and was an independent risk factor for mortality (OR 2.19 IC: 1.38-3.48 for glucose < 60mg/dL and OR: 2.26 IC: 1.15-3.26 for glucose < 40mg/dL)[15]. A meta-analysis of all the available trials did not also found any difference in mortality between intensive insulin therapy vs. conventional control (OR: 0.93 IC: 0.85-1.03).[16]

What could explain the conflicting results among the trials? First, different targets for glucose in the control groups were aimed. The trials designed to achieve a glucose range between 180-200mg/dl in the control group had more impressive results than those who achieved a glucose range between 140-180mg/dl. Second, the incidence of hypoglycemia varied greatly among the trials, and in some studies it was an independent risk factor for death.

Therefore, one may hypothesize that, perhaps keeping glucose levels in mid-range (approximately 140-150mg/dl), significant benefits could be achieved without imposing a significantly increased risk of hypoglicemia. Thus, the tricky question imposed by the results of recent clinical trials is not if glucose control should be applied, but rather how to target levels that may improve outcomes with a low rate of adverse events.

Lessons from the outpatient diabetes trials

Systemic inflammation and glucose cellular toxicity are major features in the development of vascular disease and organ failure in diabetic patients[17]. A low, but constant, degree of systemic inflammation over many decades lead to the well described endothelial activation and lesion and the consequent organ failure. This has a nice parallel with ICU patients. Severe acute illness frequently triggers a huge systemic inflammatory response[18] and increases in glucose levels.[6] This accelerated and massive inflammation leads to endothelial activation, mitochondrial damage and multi-organ failure in a matter of hours.

Thus, for distinctive and obvious reasons, intensive glucose control has been a major topic of interest regarding the therapy of outpatients diabetic populations.

An important trial published in 1993 about diabetic outpatients were the Diabetes Control and Complications Trial (DCCT),[19] which demonstrated a close relationship between glucose control in type 1 diabetic patients and a lower incidence of microvascular disease. Over 1000 patients were enrolled, and a stricter glycated hemoglobin level was targeted (6.0%) for over 10 years as compared to controls (7.0 – 7.9%). The results were very important to boost new larger studies, and change the management of diabetic disease.

After the DCCT, the UK Prospective Diabetes Study (UKPDS)[20] was a larger (over 5.000 patients examined for twenty years), randomized, multicentre trial which tested if better glucose and blood pressure control could avoid progressive organ damage caused by diabetes and change morbidity and mortality. With outstanding results, the study demonstrated that a good control of macro and microvascular progressive lesions in this population was possible by maintaining glycated hemoglobin levels between 7.0 and 7.9% in the long term, making this goal widely introduced in clinical practice.

However, more recently (2008) the Action to Control Cardiovascular Risk in Diabetes Study (ACCORD)[21] attempted, with a greater sample than the previous study (more than 10.000 patients), to elucidate if there would be proportionally effect reducing glycated hemoglobin levels to 6% as compared to the control group target from 7,0% to 7,9%. The results from the ACCORD were disappointing, especially about elevated mortality in 3 years (more adverse events related mainly to hypoglycemia), the study also brought to light the discussion about the advantages of a strict protocol in the long term care in relation to risk, costs and safety of the intervention.

Therefore, there is certainly a lesson to be learned from the conflicting results of studies addressing similar issues in outpatient diabetic individuals. Such aspects should be taken into consideration when designing future trials in the ICU setting (Chart 1).

Chart 1 - Outcomes from randomized controlled trials on strict glucose control in the last decade

RCT	When	Who	Blood glucose (mg/dl)						Observed outcomes
			Control			Intervention			
			Target	Median	Hypo	Target	Median	Hypo	
NICE-SUGAR	2009	Mixed ICU N= 6,030	<180	144	0.5%	80 - 108	114	6.8%	Higher mortality in strict control
van den Berghe	2006	Medical ICU N= 1200	180 - 200	150	3.1%	80 - 110	115	18.7%	Reduced morbidity. Reduced mortality when LOS >3 days in strict control
van den Berghe	2001	Surgical ICU N=1548	180 - 200	153	3.2%	80 - 110	103	5.1%	Reduced mortality in strict control
GluControl	2006	Mixed ICU N = 1082	140 - 180	144	2.7%	80 - 110	118	8.7%	Stopped early
VISEP	2008	Severe sepsis N=537	180 - 200	151	4.1%	80 - 110	112	17%	Increased risk for serious adverse events in strict control Stopped early
DIGAMI	2005	Diabetic and AMI N=1253	126 - 180	150	NA	90 - 126	144	NA	Hyperglycemia elevated long term mortality
ADVANCE	2008	Diabetic outpatients N=11,140	HbA1 ~<7.5%	HbA1 7.3%	NA	HbA1 <6.5%	HbA1 6.5%	NA	Reduced macro and microvascular events in strict control
ACCORD	2008	Diabetic outpatients N=10,251	7 - 7.9%	7.5%	NA	< 6.0%	6.4%	NA	Increased mortality in strict control

RCT - randomized controlled trial; N - patients enrolled; HbA1- glicated hemoglobin; LOS - length of stay; Hypo - percentage of hypoglycemia; NA - not available; ICU – intensive care unit

Where do we go from here?

We believe it is important to address the results of recent RCTs evaluating glucose control in the critically ill very carefully. Current results show that there is no clinical equipoise in this issue. Rather, we should propose that glucose levels should be controlled, avoiding the permissive and harmful levels that were clinically accepted in previous decades (>180mg/dl). However, it is imperative to define the safest way to offer patients a strategy to protect their health, avoiding damages caused by both hyperglycemia and excessively tight glucose control. Therefore, it may be generally acceptable to propose that glucose targets around 140-150mg/dl should be considered the current best care. And it is also clear that subsequent studies must address subpopulations of ICU patients, with a wide spectrum of illness, and if they should have a distinct approach regarding the glucose control strategy. In the future, perhaps, with new technologies providing individualized closed-loop algorithms, we may be able to attain greatest protection against the effects of hyperglycemia with a lower incidence of adverse events. For now, we should audit the efficacy and safety of the protocols in our ICUs and aiming for a "first do no harm" approach.

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RESUMO

Na última década o controle glicêmico em pacientes críticos foi alvo de grande polêmica. Apesar de ter sido amplamente implementado na prática médica, os grandes estudos randomizados controlados obtiveram resultados bastante conflitantes, pois além de controlar a hiperglicemia, foi identificada a necessidade de se evitar os riscos da hipoglicemia, evento potencialmente grave nessa população. Dessa forma, o presente artigo se propõe a rever e avaliar de forma crítica os estudos publicados sobre controle glicêmico em terapia intensiva, propondo um novo alvo glicêmico (150 mg/dl) que seja capaz de minimizar os malefícios da hiperglicemia e ao mesmo tempo minimizar os riscos potenciais do emprego do uso de insulina de forma intensiva.

Descritores: Glicemia; Hipoglicemia/prevenção & controle; Insulina; Sepse/prevenção & controle; Cuidados críticos

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