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Introduction of Tight Glucose Control in the ICU: Hype or Evidence Based Medicine?

Author

Armand R.J. Girbes

Professor

Internist-Intensivist, Clinical Pharmacologist

University Hospital VU, Medical Centre

Amsterdam, Netherlands

arj.girbes@vumc.nl

Introduction

In 2001, Van den Berghe et al. published the results of a study, demonstrating a clinically and statistically significant fall in mortality in intensive care (IC) patients treated by intensive insulin therapy, aiming at glucose levels between 4.4 and 6.1 mmol/l. To achieve this goal, a maximum amount of 50 units/hour of insulin was given. The intervention group was compared to a control group where a glucose level up to 12 mmol/l was accepted. Above this level insulin was given aiming at a glucose level of 10,0-11,1 mmol/l. The reduction in mortality was spectacular with an absolute reduction of 3.7% (10.9% in the control group and 7.2% in the intervention group). In a subgroup of patients who remained longer than 5 days in the ICU, the reduction was even more obvious: a mortality rate of 26.3% in the control group compared to 16.8% in the intervention group. An absolute reduction of almost 10% was therefore achieved.

Beside the fact that a particular feeding protocol may have played a role in the results of this singlecentre study, the most important criticism was on the case-mix of the studied population, of which 63% were cardiac surgery patients and only 5% were non-surgical patients. This study was nevertheless the reason for a huge enthusiasm in the IC community and many ICU's introduced a protocol for tight glucose control. However, most ICU's were not that successful in terms of achieving glucose control (Fraser et al. 2006; Vriesendorp et al. 2006; Polderman and Girbes 2006).

In the international directives for the treatment of severe sepsis, the Surviving Sepsis Campaign (SSC), recommendations were given for glucose control with levels < 8.3 mmol/l, despite the fact that the beneficial effects of tight glucose regulation on mortality have not been shown in septic patients (Dellinger et al. 2004). The target glucose levels advocated by the SSC were expert-opinion based and were higher than in the original study by Van den Berghe, in order to reduce risk of hypoglycaemia.

In 2006, the same group from Leuven published a similar intervention trial in non-surgical patients. In the total population no effect of intensive insulin therapy on mortality could be detected (Van den Berghe et al. 2006). Moreover, an excess mortality trend was present in patients from the intervention group, staying less than 3 days in the ICU. Additionally, in the intensive insulin intervention group, the risk of hypoglycaemia (glucose < 2.2 mmol/l) increased by a factor of 6 and was recognised as an independent risk factor for mortality. In a predefined subgroup with an ICU stay > 3 days, however, mortality was significantly reduced compared with the intervention group: 38.1% versus 31.3%. The latter study is therefore a negative study in terms of mortality reduction, demonstrating no beneficial effects of intensive insulin therapy versus accepting blood glucose values to 12 mmol/l.

Other Studies

In a recent German multi-centre study (The German Competence Network Sepsis), which to date, was exclusively published as an abstract, no effect of intensive insulin therapy in 488 patients with severe sepsis could be detected (Brunkhorst et al. 2005). However, serious hypoglycaemia (glucose < 2.2 mmol/l) was found in 12.1% of patients in the intervention group and in only 1.2% of patients in the control group. Despite these results, this study was underpowered for mortality and terminated prematurely. A European multicentre study, the Glucontrol trial, was also stopped early because of a high prevalence of hypoglycaemia. An Australian/New Zealand/Canadian study is underway, called NICE-SUGAR, and results are expected soon.

Euphoria and Contemplation

With all these data in mind, a contemplation on the introduction of tight glucose control as standard care in the ICU seems appropriate. Many ICU's have over-enthusiastically introduced the target glucose control as defined by Van den Berghe et al. It has even been suggested that the percentage of glucose levels within this target be included as an indicator of quality of care in the Netherlands (de Vos et al. 2006). Taking glucose regulation as an indicator for quality of care should not be coupled in any case to the target levels as indicated in the studies from Leuven. Several publications point at the danger of hypoglycaemia, although not unequivocally associated with mortality and shortterm complications (Vriesendorp et al. 2006). On the other hand, it is surprising how easily the data from the 2001 study from Leuven has been extrapolated. A closer analysis of that study shows, for example, a high mortality in the control group, particularly in cardiac surgery patients. In this group of patients mortality was as high as 5.1%. In a similar case mix of 16,349 cardiac surgical patients, coronary surgery and valve surgery, from the National Intensive Care Evaluation (NICE) database in the Netherlands, mortality was 2.3% (de Jonge, NICE Foundation). This is entirely similar to the mortality in the intervention group from Leuven. It might therefore be suggested that conclusions on the effect of intensive insulin therapy, are more a consequence of the relatively high mortality in the control group, and not due to a low mortality in the intervention group.

Relatively little attention had been given to the role of possible bias. It can be argued that more attention was paid to patients in the intervention group in this obviously unblinded study. But, combining all available data and pathophysiological understanding, it is more than reasonable to control high levels of glucose. It is also appropriate to acknowledge that Van den Berghe et al. compared only a strategy of accepting glucose levels up to 12 mmol/l to a target of 4.4-6.1 mmol/l. It is apparent that aiming at lower glucose values induces a higher risk of hypoglycaemia with its' associated complications, just as accepting high levels of glucose levels has its' own danger of complications. The favourable effect of glucose control can therefore be considered as a J-curve for the optimal glucose level (Figure 1). The question remains whether hypoglycaemia is an independent risk factor, or rather a risk marker. Hypoglycaemia as risk marker could be the result of being a reflection of serious illness of the patient, and that the secretion of counter regulating hormones is insufficient. But hypoglycaemia does not contribute causally to mortality per se. Another possibility is that hypoglycaemia is a secondary symptom of administering insulin that in itself contributes to mortality. Finally, it is conceivable that hypoglycaemia is causally related to mortality, although existing data has failed to clarify this thus far.

Conclusion

Given the results of the recent studies, intensive insulin therapy aiming at glucose levels between 4.4 and 6.1 mmol/l cannot be considered as standard care in ICU patients. The risk of hypoglycaemia is increased and repeated multi-centre studies have not confirmed the results of single centre studies. It is possible that the NICE-SUGAR study will bring new insights to the debate. In my opinion, intensive insulin therapy has been embraced with too much eagerness and some contemplation and reluctance is more appropriate.

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