Commentary

Is there more to glycaemic control than meets the eye?

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Abstract

Tight glycaemic control has emerged as a major focus in critical care. However, the struggle to repeat, improve and standardize the results of the initial landmark studies is ongoing. The prospective computerized glycaemic control study by Shulman *et al*. highlights two emerging and often overlooked aspects of intensive insulin therapy protocols beyond simple glycaemic performance. First, the clinical ergonomics and ability to integrate into the critical care unit workflow must be considered as they may impact results and definitely affect uptake. Second, the real lessons of any protocol's performance are likely to be best realized by comparison with other results, a task that is very difficult without a consensus method of reporting that allows such comparisons across studies. Embracing these issues will take the field closer to accepted, repeatable approaches to tight glycaemic control.

That tight glycaemic control in critical care saves lives is increasingly less questioned. In contrast, the *how* and *for whom* remains quite elusive. In this journal, Shulman *et al*. [1] report the results of another prospective glycaemic control study utilizing a computerized protocol to implement a relatively complex protocol.

Tight control has been of great interest since the landmark studies of Van den Berghe *et al*. [2,3] and Krinsley [4]. At least two to three further, large, randomized trials have been started, including the ongoing Normoglycemia in Intensive Care Evaluation (NICE)-Survival Using Glucose Algorithm Regulation (SUGAR) studies [5], and the discontinued Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study [6]. Finally, several prospective studies, primarily focused on developing new protocols, have been published, to the extent that reviews have recently appeared [7-9].

Two common themes emerge that are also evident in this study. The first concerns the impact of clinical burden on the results obtained. The second is one of performance. What defines good performance, and what level is required to achieve the mortality and economic [10,11] outcomes of the landmark studies?

The clinical burden of intensive insulin therapy (IIT) has not gone unnoticed [12,13]. Shulman and colleagues, have uniquely addressed this issue directly by tracking compliance in the timing of glucose measurements and thus perhaps compliance and performance in control. Only 53% (interquartile range: 41 to 67%) of glucose measurements were performed in the specified one to two hour timeframe, including a 50% (30 to 60 minutes) buffer. This result is unique in the field and clearly shows for the first time the difficulty of integrating any protocol into the typically hectic intensive care unit (ICU) environment.

In contrast, Van den Berghe *et al*. [2,3] utilized additional staff to reduce burden and avoid contamination across their randomized trial. The higher average glycaemic control obtained by Krinsley [4] without such extra staffing thus indicates the (potential) impact of clinical burden on performance. This paper thus clearly highlights the little addressed issue of human factors and the need to consider them explicitly in protocol design – perhaps including experts in the field – to obtain more consistent results. More succinctly, it may not be the protocol but the ability to implement it effectively that prevents success in some cases.

Regarding performance, patients in this study were in the target 4.4 to 6.1 mmol/L band, a median of 23.1% (15.4 to

ICU = intensive care unit; IIT = intensive insulin therapy; NICE-SUGAR = Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation [studies]; VISEP = Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis [study].

29.1%) of the time, with a further 48.5% (36.9 to 60.8%) in the 6.2 to 7.99 mmol/L band. The authors conclude that the protocol "did not achieve tight glycaemic control for a substantial portion of each patient's stay". However, their results are similar in average value and tighter in distribution than the very successful results of Krinsley [4], based on values estimated from Figure 2 and Table 4 in Krinsley's original work [4] and the data presented by Shulman *et al*. They are also similar to other studies [14-16].

This contradiction illustrates the almost complete inability to assess or compare performance consistently across studies. A review of 24 studies [7] shows that five use percentage time in a single band, while most others use a mean value and standard deviation. Target range and measurement frequency also varied considerably. Combined with differences in cohort and critical illness, it is very difficult to take significant lessons away from many of these studies. This is not a fault of the study authors or implementation, but a lack of a consensus means of reporting.

Shulman *et al*., provide significant insight into their results compared to many others, reporting percentage time in bands on a per patient basis as well as indicating the variability across the cohort via the box and whiskers plot of Figure 2. From this data and Table 4 it is possible to determine both median and variability on a per patient basis – the same basis on which tight control has a clinical impact. It is also something not reported in most similar studies, making this study unique for its transparency. Variability is particularly important as a recent study of over 7,000 patients showed that the glycaemic variability is an independent predictor of mortality [17], and thus a potentially critical performance measure.

In contrast, almost all studies report glycaemic control in terms of overall results, rather than per patient. Thus, one could (in extreme) report relatively wide variability for a protocol, when in fact each patient was tightly controlled within that range – or vice versa. Shulman *et al*.'s complete and transparent per patient reporting is a stronger template on which to make comparisons and derive lessons learned.

Thus, a second clear outcome highlighted by this study is the need for a consensus statement with regard to reporting glycaemic control performance. A better understanding would result from specifying a minimum standard that included per patient and overall results for a series of accepted glycaemic ranges and thus variability. This call is not necessarily new [18], but perhaps bears repeating.

More succinctly, a standard method of reporting results would enable easier comparison across studies and cohorts, with an ultimate goal of enabling better understanding of what performance metrics (time in band, variability, etc) are important. Coupled with improved ergonomics and integration into typical ICU environments, the potential to create consistently repeatable results will increase, potentially substantially. And thus, we might well be able to begin answering the difficult questions of *how* and *for whom*".

Competing interests

The authors have also published and done research extensively in the field of IIT protocol design.

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