Review

Health technology assessment review: Computerized glucose regulation in the intensive care unit - how to create artificial control

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Abstract

Current care guidelines recommend glucose control (GC) in critically ill patients. To achieve GC, many ICUs have implemented a (nurse-based) protocol on paper. However, such protocols are often complex, time-consuming, and can cause iatrogenic hypoglycaemia. Computerized glucose regulation protocols may improve patient safety, efficiency, and nurse compliance. Such computerized clinical decision support systems (CDSSs) use more complex logic to provide an insulin infusion rate based on previous blood glucose levels and other parameters. A computerized CDSS for glucose control has the potential to reduce overall workload, reduce the chance of human cognitive failure, and improve glucose control. Several computer-assisted glucose regulation programs have been published recently. In order of increasing complexity, the three main types of algorithms used are computerized flowcharts, Proportional-Integral-Derivative (PID), and Model Predictive Control (MPC). PID is essentially a closed-loop feedback system, whereas MPC models the behaviour of glucose and insulin in ICU patients. Although the best approach has not yet been determined, it should be noted that PID controllers are generally thought to be more robust than MPC systems. The computerized CDSSs that are most likely to emerge are those that are fully a part of the routine workflow, use patient-specific characteristics and apply variable sampling intervals.

Introduction

There is widespread consensus [1] that hyperglycaemia should be treated with insulin in patients in the ICU, although appropriate glucose levels achieved through glucose control (GC) are still under debate. Insulin therapy in ICU patients, even with a moderate glucose target range, is complex and time consuming, particularly since insulin-induced severe hypoglycaemia should be avoided. In most ICUs, protocols for GC are paper-based and nurse-driven. However, even with this form of standardization medication errors frequently occur and play a major part in overall patient safety, which is a key issue in all healthcare systems. For safety and efficiency, computerized clinical decision support systems (CDSSs) appear to be superior to standard paper protocols. Patient data management systems and computerized physician order entries are increasingly being used in the ICU, both with and without decision support. This review focuses on the progressively more complex approaches that have recently been introduced to achieve GC. Successful implementation of computer-guided GC is of relevance to other ICU domains, since the basic titration principle behind GC (for example, increase insulin infusion if glucose is high) holds for numerous other clinical ICU problems. Although this is not a formal exhaustive review, this paper discusses several important studies on paper protocols and development of computer assisted methods, including flowcharts, Proportional-Integral-Derivative (PID) and Model Predictive Controllers (MPC).

Glucose control with paper protocols

Hyperglycaemia frequently occurs in critically ill patients and is strongly associated with adverse outcome in patients with acute myocardial infarction [2], stroke [3], and trauma [4,5]. Also in a heterogeneous ICU population hyperglycaemia was associated with increased hospital mortality [6,7]. This observation raised the interesting question of whether normalizing blood glucose (BG) improves outcome. In 2001 van den Berghe and colleagues [8] showed a one-third mortality reduction in surgical ICU patients treated with

BG = blood glucose; CDSS = clinical decision support system; CGMS = continuous glucose monitoring system; GC = glucose control; MPC = Model Predictive Control; PID = Proportional-Integral-Derivative.

intensive insulin therapy (using a paper protocol for insulin infusion). However, subsequent high-quality controlled trials [9-11] and a large cohort study [12] in both medical and surgical ICU patients could not replicate this mortality benefit. The recently published international NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation - Survival Using Algorithm Regulation) trial [13] demonstrated in 6,104 patients that 'tight' GC with a target of 4.5 to 6.0 mmol/L was associated with a higher mortality. The investigators used a computer-assisted glucose regulation protocol. In the meta-analysis that followed (including the NICE-SUGAR study data), no mortality benefit was demonstrated in the tight glycemic control group [14]. However, because there is consensus about avoiding serious hyperglycaemia, GC in ICU patients is still recommended so that glucose levels should be kept at approximately <8.0 mmol/L [1,13].

To achieve desired glucose levels, insulin therapy is required in most ICU patients. GC requires intensive monitoring of glucose levels with frequent adjustments of insulin therapy. A first step in managing GC is the use of protocols that allow physicians and nurses to decide unambiguously how much insulin should be administered. The recommendations of these protocols are generally based on previous glucose levels and insulin dosing according to a 'sliding scale' protocol (a predetermined amount of insulin is administered according to the actual BG) or 'dynamic' protocol (the dosage of insulin is changed by a certain amount, according to the actual BG) [15]. Given the frequency of BG sampling, it rapidly became apparent that the nurses who care for the patient should have a central role in executing GC. Standardizing GC by a nurse-managed protocol has been found to improve safety and efficiency of GC [16].

Hypoglycaemia

One of the main challenges in achieving glycaemic control is minimizing the risk of hypoglycaemia. Hypoglycaemia can cause serious complications and should be prevented in critically ill patients [17]. In several studies an increased occurrence of severe hypoglycaemia was strongly associated with tight glycemic control. Two large trials investigating the clinical effects of strict GC that were prematurely ended showed high rates of iatrogenic hypoglycaemia [10,11]. Although the overall evidence suggests that the beneficial effects of insulin therapy may outweigh the possible negative effects of hypoglycaemia [18], fatalities occurring due to iatrogenic hypoglycaemia are not acceptable. A balance must be struck between the preferred level of control and the number of measurements. To achieve GC with a low incidence of hypoglycaemia without excessive BG sampling, more complex computer supported algorithms are required that manage the patients with an increased risk for hypoglycemia.

Introduction of computerized glucose control

For many years, computer software has been recognized as a promising tool to improve clinical practice as many adverse events can be traced back to preventable human errors. These so-called CDSSs are information systems designed to improve clinical decision making using characteristics of the individual patient. Implementations of these systems have been shown to reduce serious medication errors [19] and improve adherence to recommended care [20]. In the past few years several computer directed glucose regulation programs have been investigated for their effectiveness and safety in critically ill patients. We performed a literature search (PubMed, Cochrane and Medline) to find published computer-based intravenous insulin protocols that were designed for critically ill patients and tested in an ICU setting (in at least 15 patients). Table 1 summarizes the 19 identified studies [13,21-38].

How to create artificial control?

Devising an algorithm for controlling blood glucose is a challenging task. The algorithm should be evaluated to be safe, robust and efficient for a population of patients with a wide range of clinical conditions. To date, three types of algorithms have been considered for BG regulation: (heuristic) paper-based or equivalent computerized flow-charts, PID and MPC.

Computerized flowcharts

The first flow-chart protocol was based on studies by van den Berghe and colleagues [8,9]. It allows nurses to determine (at the bedside) the necessary adjustment of the insulin pump based on the most recent BG value and the trend (using the number and levels of past BG values to determine the trend). In case of extremely low BG or other exceptional cases, special actions are planned. The paper-based flow-chart protocol can easily be converted into a computerized form (see, for example, Thomas and colleagues [36] and Laha and colleagues [28]). Furthermore, the use of computers allows an increase in the sensitivity (resolution) of the titration part, for example, in the Vanderbilt protocol [21]. The formula uses a simple multiplier, which is determined and adjusted according to previous BGs (BG in mmol/L; multiply multiplier by 18 for BG in mg/dl):

$$\text{Insulin dose (U/h)} = \text{Multiplier} \times (\text{BG} - 3.3) \quad \text{(Equation 1)}$$

where the multiplier is adjusted by 0.01 up or down when two consecutive BGs are above 6.1 or below 4.4 mmol/L, respectively; in the case of extreme values (<3.3 or >11 mmol/L) the multiplier is adjusted by 0.02, and in the case of BG <3.3, the insulin dose becomes zero. Boord and colleagues [21], and later Dortch and colleagues [24], demonstrated an improvement in overall GC compared to a previous manual protocol. At the same time, a glucose sample was required approximately 18 times per day.

PID control

A titration formula like Equation 1 puts the control algorithm in the class of the so-called PID controllers. These are the most

Table 1

Summary of published computer-assisted glucose regulation protocols, designed for critically ill patients

Reference	N	Patient type	APACHE II	Target range (mmol/L)	Performance	Hypoglycaemia[a]	Measurements per patient per day
Boord *et al.* [21]	204	Surgical ICU	?	4.4 to 6.1	49% of time in range	0.2% <2.2 mmol/L	~18 (12 to 24)[b]
Cordingley *et al.* [22]	16	Mixed ICU	16.6	4.4 to 6.1	63% of time in range	0 <2.2 mmol/L	10.9
Davidson *et al.* [23]	5,808	General medical and surgical floors	?	Variable	'Stable glucose'	0.6% <2.8 mmol/L	~18 (12 to 24)[b]
Dortch *et al.* [24]	243	Trauma ICU	ISS 27.5	4.4 to 6.1	42% of measurements in range	0.2% <2.2 mmol/L	10.7
Hermayer *et al.* [25]	66	CABG	?	4.4 to 6.7	Mean BG 6.4 mmol/L	0.10% <2.2 mmol/L	16.2[c]
Horovorka *et al.* [26]	30	Cardiac surgery	?	4.4 to 6.1	60% of time in range	0 <2.9 mmol/L	16
Juneja *et al.* [27]	2,398	Mixed ICU	?	4.4 to 6.1	61% of measurements in range	0.4% <2.8 mmol/L	~18 (12 to 24)[b]
Laha *et al.* [28]	661	Mixed ICU	16	4.5 to 7.2	95% of measurements in the range 3.7 to 12.1 mmol/L	1.7% of patients with a single episode <2.2 mmol/L	~12 (6 to 24)[d]
Meyenaar *et al.* [29]	179	Mixed ICU	13	4.5 to 7.5	53% of time in range	0.05% <2.2 mmol/L	3.4
Morris *et al.* [30]	775	Mixed ICU	21.8	4.4 to 6.1	42% of measurements in range	0.33% <2.2 mmol/L	~12 (6 to 24)[d]
NICE-SUGAR [13]: intensive control	3,054	Mixed ICU	21.1	4.5 to 6.0	Mean time-weighted BG 6.4 mmol/L	6.8% <2.2 mmol/L	~12 (6 to 24)[d]
NICE-SUGAR [13]: conventional control	3,050	Mixed ICU	21.1	8.0 to 10.0	Mean time-weighted BG 8.0 mmol/L	0.5% <2.2 mmol/L	~12 (6 to 24)[d]
Pachler *et al.* [31]	25	Medical ICU	26.6	4.4 to 6.1	HGI = 0.4 mmol/L	1 episode <2.2 mmol/L	12.3
Plank *et al.* [32]	30	Cardiac surgery	11.4	4.4 to 6.1	52% of time in range	0 <2.2 mmol/L	24
Rood *et al.* [33]	66	Mixed ICU	19.5	4.0 to 7.0	54% of time in range	0.09% of time <2.5 mmol/L	9.9[c]
Saager *et al.* [34]	20	Cardiac surgery	?	5.0 to 8.3	84% of time in range	5 episodes <3.3 mmol/L	24
Shulman *et al.* [35]	50	Mixed ICU	23	4.4 to 6.1	23% of time in range	0.04% of time <2.2 mmol/L	12.7
Thomas *et al.* [36]	603	Mixed ICU	14.4	5.4 to 7.1	85% of measurements <8 mmol/L	19 episodes	~12 (6 to 24)[d]
Toschlog *et al.* [37]	128	Trauma	ISS 24.5	4.4 to 7.2	Mean BG 6.4 mmol/L	32% of patients with a single episode <2.8 mmol/L	?
Vogelzang *et al.* [38]	2,800	Mixed ICU	14	4.0 to 7.5	67% of time in range	0.04% <2.2 mmol/L	5.9

[a]Hypoglycaemia is represented as the proportion of all measurements, unless otherwise specified. [b]No exact data, but protocol has 'hourly to two-hourly measurements'. [c]Calculated from number of measurements and length of stay. [d]No exact data, but protocol has 'hourly to four-hourly measurements'. APACHE, Acute Physiology and Chronic Health Evaluation II; BG, blood glucose; CABG, coronary artery bypass grafting; HGI, hyperglycaemic index; ISS, Injury Severity Score; NICE-SUGAR, The Normoglycaemia in Intensive Care Evaluation - Survival Using Algorithm Regulation.

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widely used controllers in industrial applications. Typical examples are the kitchen furnace and automotive cruise control. The basic idea of PID control is easy to explain: deviation of the controlled quantity (BG in our case) from the target is corrected by adapting the control parameter (insulin) using a linear combination of absolute deviation, trend, and the sum of past deviations. In fact, a PID controller has already been used in the BioStator, the first device for 'glucose clamping', developed in the late 1970s [39]. Equation 1 utilizes only the proportional (P) part of the PID control. Vogelzang and colleagues [38,40] also use the derivative (D) component. For the rationale behind the application of the integral (I) part, see Wintergerst and colleagues [41].

Model predictive controllers

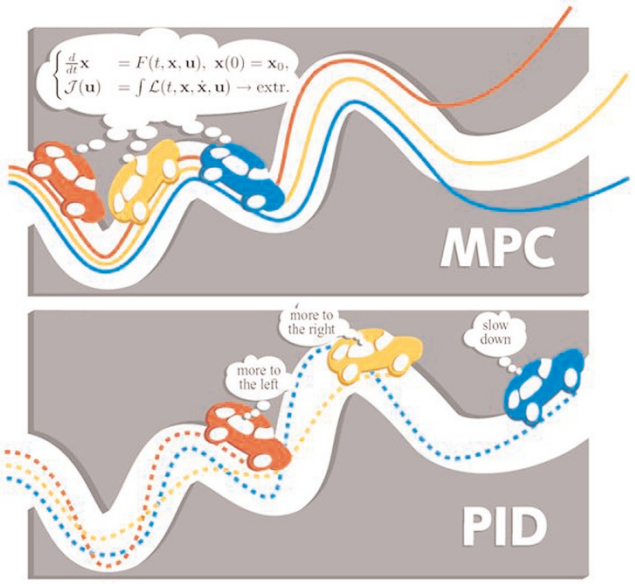
A great deal of work has been invested in mathematical modelling of glucose regulation. Models of various complexities have been constructed in the past 50 years, as recently comprehensively reviewed by Chee and Fernando [42]. Deterministic mathematical models can also serve as a basis for the development of control algorithms. Given the model equations and the values of all model parameters, one is able, in principle, to precisely compute the glucose evolution in response to any insulin infusion strategy. In theory, this allows a selection of an optimal insulin infusion scenario. In practice, however, mathematical models rarely exactly describe reality, and a large number of parameters need to be estimated, which will inevitably lead to errors in prediction of glucose response.

An example of such complex MPC was developed by the CLINICIP (Closed Loop Insulin Infusion in Critically Ill Patients) group. The ultimate goal is a closed loop system for glycemic control. Plank and colleagues [32] describe, in a multicenter randomized controlled trial, glucose management with the MPC program in 30 patients after cardiac surgery. Compared with routine protocols for glucose regulation, the time within target range improved significantly (19% to 52%) during the first 24 hours postoperatively. However, an hourly glucose sample was necessary, which substantially increased the workload of the ICU nursing staff. Thereafter, the algorithm was enhanced with a variable sampling interval based on the accuracy of the glucose prediction. The improved protocol (eMPC) resulted in a 50% drop in sampling frequency [31] and maintained effective glucose control in different ICUs, with different (nutritional) protocols and during cardiac surgery [22,26]. The authors report that the program was safe in 30 patients. It should be noted, however, that the published incidence of hypoglycaemia, a key safety indicator, varies from less than 1% to a few percent, thus rendering a sample size too small to assess such a safety parameter.

PID versus MPC

The following might serve as a caricature explanation of the difference between PID and MPC. Suppose a person wants to drive a car on a mountain road. The control (equivalent to the art of driving) consists of two continuous inputs: steering and throttle. The PID approach would be analogous to a driver negotiating the road by continuously adjusting the input parameters, correcting deviation from the ideal line, proceeding along as the new corners or obstacles appear in front. The MPC strategy would be analogous to studying the whole road and selecting the driving strategy before the departure. Note that even the MPC approach does not guarantee 100% success as the strategy might have to be adjusted to changing conditions like rain, other road users, and so on. This example is illustrated in Figure 1.

Figure 1



Model Predictive Control (MPC) versus Proportional-Integrate-Derivative (PID) control. When using MPC control, the driver determines ('calculates') his driving strategy before departure after careful investigation of the road. When he uses the correct information (input variables), he stays on the road (yellow car), but small errors in input variables can lead the car in the wrong direction (red and blue cars). The drivers using PID control readjust their driving strategy often by frequently calculating the difference with the 'ideal' track.

The theoretical advantage of the MPC over the PID approach is that the 'intelligent' control algorithm could be able to minimize glucose oscillations and keep glucose within the target range better than PID controllers. This, however, would require further improvement of not only the mathematical models and the parameter estimation procedures, but the control algorithms as well, since the current results of *in silico* (that is, with a virtual electronic patient) testing exhibit rather dramatic oscillatory behavior [43].

Finally, some believe that with the envisioned introduction of continuous glucose monitoring systems (CGMSs) in the ICU setting, the current problem - high workload for nurses

resulting from frequent glucose measurements - will reduce considerably. Results reported in the literature strongly suggest that, with the frequent sampling of BG, the more transparent PID controllers are fully capable of regulating glucose successfully. However, application of CGMSs in the ICU setting is still hampered by a relative inaccuracy of the existing sensors. Moreover, it must be noted that regardless of the algorithm employed, CGMSs may not come so easily or cheaply as originally envisioned, since the devices are expensive and may require quite frequent BG samples as well, albeit only for calibration purposes. For more discussion on the combination of CGMSs and PID controllers or PID control versus MPC control see [44-48].

Computer versus paper-based insulin infusion protocols

Whether computer-based or paper-based, the underlying algorithm is the crucial 'know-how' responsible for overall performance. The same algorithm in paper or computer form should have the same overall performance, provided that nurses are easily able to use both versions and comply with recommendations in the same way. Computer implementations probably offer higher comfort to the nursing staff. The chance of human error grows dramatically with the complexity of the protocol when it is implemented on paper. Therefore, the class of all protocols potentially implementable by humans is strictly smaller than the class of protocols implementable on the computer.

Successful implementation of decision support systems

To make the implementation of a computerized CDSS successful, the algorithm used is not the only element that must be taken into account. Kawamoto [49] performed a systematic review to identify features critical to the success of a CDSS and concluded that to make a program likely to succeed, it must be fully part of the caregivers' routine workflow and provide the decision support at the time and location of the actual decision making. Also transparency, such as documentation of the reasons behind the decision making, and a feedback mechanism (for example, an alarm as a reminder for when a glucose sample is required) were features leading to success. Before implementation, adequate training of the nursing staff and physicians is important. To date, no systematic studies on the costs of computerized protocols have been published, but it is likely that a program that requires 18 measurements per day will turn out to be more expensive than one that requires 6 measurements per day.

Future perspectives

To improve patient safety, more and more technology will arise in healthcare, especially in the ICU, where the complexity of patient care is high. A system that is effective, safe, transparent and easy to work with has a chance to become routine practice. An advantage of computerized regulation is that improvements of the internal algorithm may enable a higher level of control and safety while maintaining a simple user interface. To date there have been no direct comparisons made between different algorithms, so the best approach has not been determined yet. Development of a closed-loop system using continuous BG measurements has been ongoing for many years. For the near future, the method of choice for insulin therapy will still be based on intermittent glucose sampling because the continuous techniques are not yet reliable enough (mainly in the hypoglycaemic area) and are expensive.

Conclusion

Computer-assisted glycemic control has proven to be more safe and effective than paper protocols in ICU patients. A successful system is nurse-centered, fully integrated into the routine workflow, transparent, and uses patient-specific information with intermittent glucose measurements and variant sampling intervals.

Competing interests

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