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VIRTUAL TRIAL AND MONTE CARLO ANALYSIS OF MODEL-BASED GLYCAEMIC CONTROL PROTOCOL WITH REDUCED NURSING EFFORT

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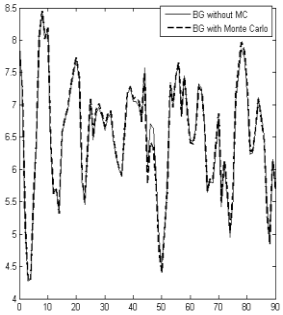
Graphical abstract



BG levels with and without MC error of a random patient

Abstract

Tight glycaemic management has been shown to be beneficial to the outcomes of patients receiving intensive care. However, tight glycaemic control (TGC) protocol within intensive care (ICU) comes with a high clinical demand, namely high nursing effort. Thus, there is a need for a protocol that is safe, effective, robust, yet does not require a high nursing effort. A less intensive protocol is designed to use a combination of subcutaneous long-acting insulin (glargine) with IV insulin bolus and only requires blood glucose (BG) measurements every 4 hours while maintaining measurement within 4.0-6.1 mmol/L.

Keywords: Monte Carlo, model-based protocol, stress hyperglycaemia, glargine, nursing intervention

Abstrak

Pengendalian kawalan paras gula darah secara ketat berjaya menunjukkan impak yang baik terhadap pesakit di Unit Rawatan Rapi. Akan tetapi, pengendalian secara ketat ini memerlukan usaha yang tinggi daripada jururawat dan doctor. Oleh itu, protokol yang selamat, efektif, teguh dan pada masa yang sama tidak memerlukan usaha tinggi perlu diusahakan. Protokol kurang intensif dicadangkan dengan menggunakan insulin glargine secara subkut dan insulin IV. Kekerapan pengambilan sampel darah juga dikurangkan kepada setiap 4 jam dimana paras gula darah dikekalkan secara ketat 4.0-6.1mmol/L.

Kata kunci: Monte Carlo, protocol berasaskan model, glargine, intervasi jururawat.

1.0 INTRODUCTION

Implementation for minimal taxing nursing effort with long-acting insulin protocol has become a prominent issue for the management of hyperglycaemic patients in intensive care unit (ICU) [1]. Stress hyperglycaemia is a condition that often occurs among ICU patients where blood glucose (BG) is elevated even for patients without prior history of diabetes. The adverse effects from hyperglycaemia, hypoglycaemia or even the variability of glycaemic level itself are a concern of many. These patients may be at higher risk of inflammation, stroke, cardiac arrest and at worst mortality [2]. According to American Diabetes Association, stress hyperglycaemia is categorised with fasting BG of more than 6.9mmol/L or random BG of more than 11.1mmol/L. Controlling BG levels involves a lot of effort, among which are frequent monitoring and recording of BG measurements, administration of insulin infusion or bolus and adjustments of feed rate. Apart from that, nurses need to continuously monitor patient's

response toward treatments, give medications and to provide overall care which involves extensive hours [1]. Within ICU, patient's glycaemic level often varies especially during early admission as no proper glycaemic control has taken place. Proper management of tight glycaemic control (TGC) has been associated with lower risks of infections and mortality, lower period of ICU stay, lower case of ICU rebound and lower hospital costs. Although the right level of glycaemic band is still debated, the need of glycemic management has been widely agreed and accepted. This resulted in a lot of initiatives where protocols or ICU guidelines have been developed if not improvised with various range of TGC for treating hyperglycaemic patients [3-4].

One way to establish a control protocol within ICU is through model-based method. Model-based protocols deliver patient specific control where the glycaemic control protocol can be devised individually. Through model-based methods, virtual trials are carried out to design or develop protocols in-silico. Herewith attention to reduce intervention frequency or incurred nursing effort may be evaluated and devised. Glycaemic control protocol may be optimized virtually to save time, money and most importantly to yield a better patient outcome.

The protocol developed in this study is established from SPRINT [5] but updated with a lesser intervention in terms of BG measurement frequency and lesser insulin bolus amount. SPRINT protocol is a simple wheel-based system that modulates both insulin and nutritional inputs feed rate hourly to maintain BG levels within the desirable range of 4.0-6.1 mmol/L. The doses from SPRINT are given according to patient-specific insulin sensitivity. The new protocol simulated in this study is a combination of an updated SPRINT and a long-acting insulin, glargine. Glargine has been used for treatment of Type 1 and Type 2 diabetic patients and proves to be an effective basal insulin. It mimics the basal secretion of insulin from pancreas with no definite peak. The absorption pattern is slow, constant, predictable and reproducible [6]. Hence, a once daily injection is enough to cover patient's basal insulin needs which in turn would help to lower nursing effort.

Understanding the need for insulin delivery protocols that can be successfully implemented with minimal clinical effort, this paper studies the robustness of the designed protocol. A Monte Carlo (MC) approach is carried out to quantify the performance and robustness of the protocols to errors, namely physiological variability and sensor errors. The main objective is to achieve low nursing frequency as compared to SPRINT clinical data while maintaining patient's overall safety.

2.0 PHARMACOKINETICS MODEL

The model used in this study integrates an insulin glargine compartment model from Wong *et al [7]* and an insulin glucose model from Lin *et al* [8].

Table 1 Virtual trial patient cohort

Demographics	Median [IQR]
Number of patients (n)	40
Female	19
Male	21
Age	59 [44 71]
APACHE II Score	19 [17 27]
Length of stay (LOS)	6 [4 11]
Mortality (1=alive;0=died)	1=37; 0=3

3.0 METHOD & MONTE CARLO SIMULATIONS

Table 1 shows the random selection details of 40 ICU patients that represent a typical group normally seen in ICU. These patients received insulin therapy under SPRINT protocol [5]. Percentage of female patients simulated is 47.5%. Median and IQR percentile of age and APACHE II score are 59 years [44 71] old and 19 [17 27]. The median of length of stay is 6 days with IQR between 4-11 days. There are 3 mortality cases in the patient cohort.

The frequency of BG measurements, changes in feed rates and IV insulin boluses are governed by the SPRINT protocol. SPRINT requires current and previous blood glucose measurements, the amount of previous hour IV insulin bolus and nutrition given in the previous hour, all to determine nutrition and insulin bolus for the next interval. The patient's time-varying insulin sensitivity metric (*SI*) was fitted to the actual clinical data using an integral fitting method [9]. Constraints are placed on *SI* to ensure it is within a physiologically valid range. The resulting time varying *SI* profiles represent time-varying metabolic status for individual patients. Testing new interventions with this profile, in simulation, provides new outputs. Thus, the profile of *SI* can be used to create "virtual patients" for testing insulin protocols.

As SPRINT operates on the basis of estimating patient's apparent insulin sensitivity, the protocol is still applicable with a background infusion. However, instead of BG measurement taken every 2-hourly when patient is stable, this protocol takes measurement 4-hourly. Patient is categorized as stable with 3 consecutive measurements within 4.0-6.1mmol/L. The recommended insulin bolus from SPRINT controller is also reduced by 1 unit in this updated protocol. Virtual trials are performed using updated SPRINT with daily dose of glargine. The dosing frequency of glargine is 24 hours, where the first dose is at 12 hours after ICU admission. The size of initial glargine bolus is the sum of SPRINT boluses administered during the previous 12 hours. The following glargine is calculated as being half of the total daily insulin (IV boluses+glargine) from the previous day. Each glargine bolus is capped at 40 U/daily for patient safety.

4.0 MONTE CARLO ERROR

150 Monte Carlo error simulations were performed per patient to generate statistics. Each virtual trial had added sensor noise simulated to be normally distributed with a standard deviation saturated max of ±20% and max error of ±4 standard deviations. This sensor error represents error from glucose meters. Glucose meters are used to measure and display the amount of BG. Variability in subcutaneous absorption is done by varying glargine parameters errors which are; fraction of glargine as precipitate, $a_{p,gla}$, glargine hexamer dissociation rate [min-1], $k_{1,gla}$ and glargine precipitate dissolution rate [min-1], $k_{p,gla}$. These variations produce possible range for time to maximal plasma insulin T*max*, and plasma insulin concentration, C*max* [mU/L]. Thus, variability is accounted for in glargine pharmacokinetics parameters and glucose sensor error. There are 6000 simulations in total (40 patients X 150 simulations), each being unique due to different random errors generated. Simulated error reflects the clinical variability, which gives a realistic feature to assess the model based control protocol. The main assessments taken into account are accuracy and repeatability. Figure 1 illustrates the model parameter variability for 150 MC simulations of glargine pharmacokinetics parameters $a_{p,gla}$, $k_{1,gla}$ and $k_{p,gla}$ of a randomly selected patient.

Safety and performance of the protocol are evaluated by avoidance of hypoglycaemia, median and IQR of BG measurements, percentage spent in desired band (4.0-6.1mmol/L), amount of insulin prescribed (IV boluses+glargine), amount of nutrition given and nursing effort intensity based on number of interventions. Specifically, nursing effort intensity is measured by the number of intervention required, which includes measuring BG levels, adjusting feed rates, administering SPRINT IV and glargine bolus.

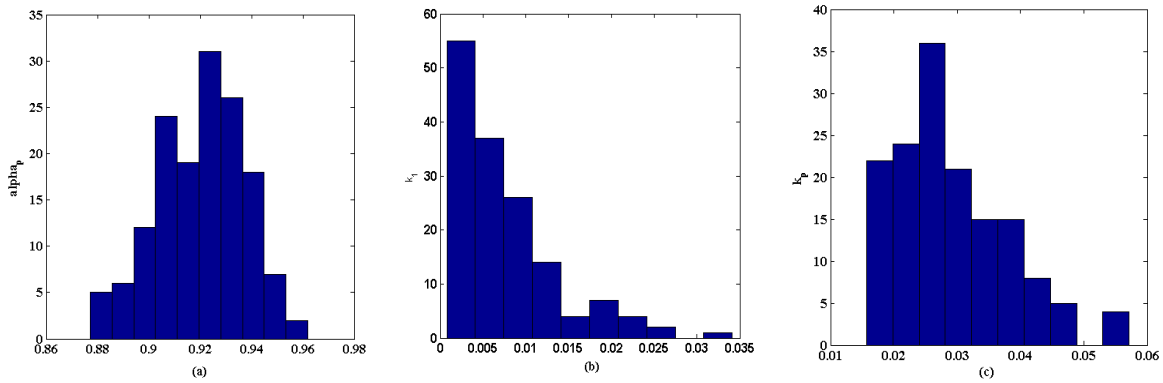


Figure 1 Histogram plot of glargine pharmacokinetics parameters with MC error simulated 150 times on a random patient (a) $a_{p,gla}$ (b) $k_{1,gla}$ (c) $k_{p,gla}$

5.0 RESULTS

Table 2 shows the simulation results of 40 patients with and without MC error as compared to SPRINT clinical data. Figure 2 gives a closer look at the BG level of a random patient throughout the ICU stay with and without MC error. It can be seen that the level of BG is not affected with the simulated MC error. Finally, Figure 3 illustrates a sample patient profile from the virtual control protocol. The first panel portrays both clinical (actual) and model simulated BG while 2nd panel shows the insulin bolus and background glargine. Panel 3 is the nutrition as recommended by the model-based control protocol while the last panel is the patient's *SI* profile. This *SI* profile is the hourly metabolic indicator used for BG, insulin and nutrition model prediction. As seen in the 2nd panel of Figure 3, it is evident there are few periods of gaps where no bolus is needed. This greatly increases patient's comfort and nurse's workload is greatly reduced. Instead of giving insulin bolus 1-2 hourly, more attention can be given to other areas that can improve overall patient care.

6.0 DISCUSSION

Due to high nursing effort, TGC implementation in ICU has not been widely practiced even though the importance of TGC is agreed. In order to replicate error typically seen within ICU, Monte Carlo captured in this study are clinical variability often seen from glucose meters and glargine pharmacokinetics parameters. Virtual simulations results show that BG measurements are not affected with the MC errors.

Table 2 Virtual trial results of Monte Carlo (MC) for 4 hour protocol

Median [IQR]	Clinical	Without Monte Carlo	With Monte Carlo
Blood Glucose [mmol/L]	5.33 [4.96 5.67]	5.39[4.99 5.89]	5.36 [4.92 5.75]
Insulin bolus [U/daily]	46.47 [39.52 51.12]	32.45[28.77 40.87]	26.03[25.43 27.25]
Glargine [U/daily]	0 [0 0]	36.91 [34.89 38.15]	33.45 [33.45 33.45]
Intervention [N/day]	39.15 [37.14 40.74]	27.25 [26.32 28.50]	25.22 [24.61 25.63]
Timeband [%]	86.80 [77.99 91.57]	80.77[72.86 85.49]	83.61 [81.43 85.29]
Feed [mu.min/L]	0.87 [0.87 1.09]	0.87 [0.79 0.87]	0.98 [0.90 0.98]
Hypo [mmol/L]	0 [0 0]	0 [0 0]	0 [0 0]

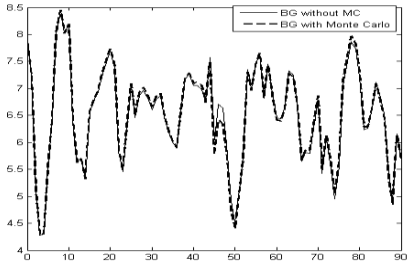


Figure 2 BG levels with and without MC error of a random patient.

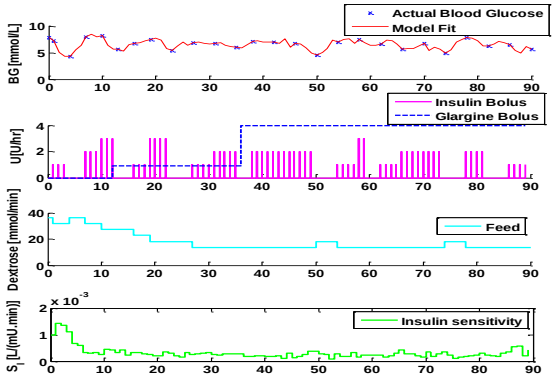


Figure 3 Random patient profile illustrating from top to bottom panel, patient's actual and model simulated BG, insulin, feed and insulin sensitivity, *SI*.

Most importantly, these results are achieved with reduced nursing effort. Nursing effort intensity is reduced from 39.15 [37.14 40.74] (N/day) to 25.22 [24.61 25.63] (N/day). This reduction of around 14 is meaningful once translated to minutes or hours saved. A study showed that for every hour nurses need to locate a glucose metre, perform a finger stick, record and adjust readings and perform appropriate rate adjustments which take around 5 minutes per patient [10]. Thus, a reduction of 14 unit is roughly 60 minutes saved.

7.0 CONCLUSION

A model-based control protocol designed for ICU glycaemic control with lower nursing effort is virtually simulated. It is intended that this protocol with robustness analysis offer a safe means to study nursing effort intensity and for protocol comparisons prior to clinical setting.

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