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Study on the blood glucose management with controlled goal feed in Malaysian critically ill patients

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Abstract. Stress-induced hyperglycaemia is commonly occurred in the intensive care unit (ICU). It is known that the intensive insulin therapy (IIT) has successfully managed the blood glucose level within the targeted band. However, modifications on the current practice need to be considered to minimize the risk of hypoglycaemia and mortality. Thus, the aim of this study is to assess the performance of a new practice known as Stochastic Targeted (STAR) Protocol in managing blood glucose levels in Malaysia ICU setting. STAR is a tablet-computer based protocols that provides patient-specific glucose control framework accounting for patient variability with a stochastically derived maximum 5% risk of hypoglycaemia events. A retrospective 92 non-diabetes patient's data who underwent IIT were identified. Patient's blood glucose levels, exogenous insulin and nutrition inputs including patient demographics were extracted from the ICU charts to create virtual patients by using physiologically mathematical model. Three trials were simulated with controlled goal feed (GF) and without GF. Only one type of nutrition is considered in this study which is Glucerna. The outcomes will be compared in terms of %BG within the targeted band of 4.4 to 10.0 mmol/L, the total number of BG measurements, and the % of severe hypoglycaemia. The results indicate that STAR virtual trial with controlled GF reduced the risk of hypoglycaemia to 3% and the clinical burden up to 1630 hours while maintaining BG within the targeted band. The total number of BG measurements also decreased to 5384 from 7038. Thus, the implementation of STAR protocol in the Malaysia ICU is beneficial and it is proven safe while aiding nurses and physicians in reducing the clinical burden and medical cost in treating stress-induce hyperglycaemia in the demanding ICU setting.

1. Introduction

Patients with acute, life-threatening illnesses that admitted to the intensive care unit (ICU) required close monitoring from the medical staff. Around 20% of mortality cases in the ICU have been reported worldwide. Most of the causes of deaths were from circulatory system disorder, renal failure and critical illness attributable to the failure of multiple organ systems [1-3]. Despite special treatment given to the

patient, their poor body is in a stress state that leads to the stress-induced hyperglycaemia incidence [4, 5].

Hyperglycaemia event is a condition where human blood glucose level is high, while in the opposite condition, where human blood glucose level lower than the normal level is called hypoglycaemia. In the intensive care unit, stress-induce hyperglycaemia occurs when the patient in a stress response where patient's hepatic glucose production increased and inhibition of insulin secretion caused by the strong counter-regulatory hormones and lead to elevation of insulin resistance and blood glucose (BG) concentrations [1, 5]. This condition has been independently related to the rate of mortality in the ICU. The undesired episode can be reduced with the control of patient's BG, despite the process is difficult due to complex, and variable dynamic stress response experienced by the patients [6].

Over the years, there are new researches and methods were introduced to the medical community, in order to control a patient's blood glucose. Currently, the most commonly used protocol is Intensive Insulin Therapy (IIT) that applied sliding scale method in determining the amount of insulin administrated to the patients based on the current measured blood glucose via finger prick. This conventional protocol, which is a manually automated system, that requires closed supervision and monitoring by the medical staffs. Furthermore, this protocol is considered as a standard protocol to control ICU patient's BG levels in Malaysia ICU.

Although IIT has been successfully maintained patient's BG level within a safety range [4], but IIT also has high possibility to lead an undesired incident such as severe hypoglycaemia event [7-9] that will lead to the increased mortality cases. The implementation of sliding scale method in managing blood glucose in the ICU is commonly in hourly-basis. In fact, this method is incapable in predicting the next hour blood glucose level given a certain amount of exogenous insulin based on the level of severity of BG measurement [10, 11]. Thus, this therapy indirectly create clinical burden in terms of monitoring and managing BG levels in the ICU setting, especially for patients with comorbidities that requires special attention from the nurses and physicians. Thus, to encounter this clinical burden and at the same time provide a safe treatment, a clinical validated protocol which has been used widely in New Zealand, Hungary, Belgium and other countries [6, 12-14] known as STAR protocol.

Stochastic TARgeted (STAR) protocol is a flexible model-based tight glycaemic control framework accounting for patient variability with a stochastically derived maximum 5% risk of BG below minimum safety requirement. This tablet-computer-based protocol provides patient-specific glucose control. It uses a clinically validated pharmacokinetic and pharmacodynamic model of the insulin-glucose system and a cohort-based model of insulin sensitivity variability to compute optimal patient-specific insulin and nutrition [14]. Since 2011, Christchurch Hospital ICU, Christchurch, New Zealand and Kalman Pandy Hospital, Gyula, Hungary currently have been using STAR protocol as their standard care in the ICU [6].

Thus, this study is mainly focused on assessing STAR performance in Malaysian ICU's cohort (specifically in Hospital Tengku Ampuan Afzan, Kuantan, Pahang, Malaysia) by using in-silico preclinical trials. Specifically, the nutrition intake will be modified by selecting only one type of nutrition i.e. Glucerna and the rate will be corrected via controlled goal feed calculation. The outcome of this study is expected to reduce the undesired effects which will improve the patient condition and to improve the current manual-automated BG control protocol to an automated system where it can reduce clinical workload and medical costs significantly [15]. The STAR protocol has been proven in delivering positive outcomes especial in reducing the mortality rate in the ICU [6, 12-14, 16-18]. Moreover, it is considerably having a high potential in Malaysia ICU setting because of the ability of STAR framework that has been proven safe with significant reductions in hypoglycaemia and mortality cases due to its characteristics, which can forward predict changes in patient's metabolic changes [16, 19, 20].

2. Methodology

2.1 Physiological Model

The real-time Intensive Care Insulin-Nutrition-Glucose (ICING) model is used to simulate a critically ill patient's BG level to identify their hourly insulin sensitivity, SI [5, 21-23]. SI is a condition where glucose content in the human blood triggers the pancreas to secrete insulin which stimulates cells to

absorb blood glucose. The model equations are defined in Equation (1) – (7) and its graphical overview is presented in Figure 1.

$$\dot{G} = -p_g G(t) - S_I G(t) \frac{Q(t)}{1 + \alpha_G Q(t)} \frac{P(t) + EGP - CNS}{V_G} \tag{1}$$

$$\dot{Q} = n_I\big(I(t) - Q(t)\big) - n_C \frac{Q(t)}{1 + \alpha_G Q(t)} \tag{2}$$

$$\dot{I} = -n_K I(t) - n_L \frac{I(t)}{1+\alpha_I I(t)} - n_I\big(I(t) - Q(t)\big) + \frac{u_{ex}}{V_I} + (1 - x_L)\frac{u_{en}(G)}{V_I}) \tag{3}$$

$$P_I(t) = -d_1 P_1 + D(t) \tag{4}$$

$$P_2(t) = -min(d_2 P_2, P_{max}) + d_1 P_1 \tag{5}$$

$$P(t) = min(d_2 P_2, P_{max}) + PN(t) \tag{6}$$

$$u_{en}(G) = min(max(16.67, k_1 G(t) - k_2), 266.67) \tag{7}$$

where the model nomenclatures can be referred as in [10].

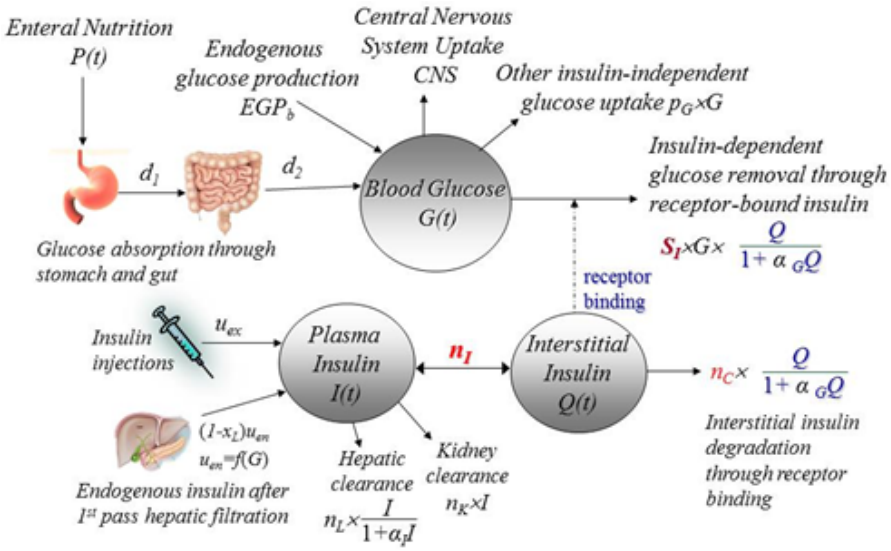

Figure 1. ICING model physiological schematic diagram [15].

Basically, the physiological model as listed in equations (1) – (7) (i.e. in Figure 1) used in this study has three main compartments which represents the blood glucose mechanism with the ability to capture the long-term dynamics and progress of a critically ill patient's glucose-insulin response. The main compartments are identified as blood glucose (G), plasma insulin (I) and plasma intersitital insulin (Q). The inputs for G in which rise the blood glucose level is through enteral nutrition given to the patients

and the endogenous glucose production (*EGP*) by the liver. In return, the glucose is used by central nervous system (*CNS*), and other insulin-dependent glucose cells. In fact, the glucose also being cleared via receptor-bound insulin through liver and kidney. Once, the blood glucose level is rise plasma insulin will be trigger and release to maintain the blood glucose in maintaining glucose homeostasis. Plasma insulin is produced from pancreas. If insulin is not enough exogenous insulin (Actrapid) will be introduced to the patient. Plasma insulin is cleared by liver and kidney after glucose homeostasis achieved. This mechanism is continuously repeated once patient consumed food or nutrition.

Moreover, this validated physiological model as listed in equation (1) – (7) known as ICING has achieved low fitting and low prediction error based on prior studies [8, 10–12, 15-17] when clinical data (blood glucose levels, nutrition and exogenous insulin inputs) obtained from the patients is fitted to ICING model.

2.2 Virtual patients

Virtual patients are simulated by using Hospital Tengku Ampuan Afzan (HTAA)'s retrospective clinical data of 92 non-diabetes patients as shown in Table 1 who underwent IIT to carry out STAR in-silico virtual trials. An hourly treatment-independent SI profile is identified through the virtual patients created from the clinical data, allowing virtual trials to realistically simulate patient response based on the given treatment.

After taking into consideration of some physiological factor, comorbidity of patients is filtered based on their previous history and patient with a history of diabetes mellitus is neglected while patient's length of stay is limited to five days.

There are two types of nutrition that are commonly given to the ICU patients: enteral and parenteral nutrition. Patients who were given parenteral nutrition are neglected in this study. The current clinical practice in HTAA used specifically five types of enteral nutrition (refer to Table 2), which are Glucerna, Jevity, Diabetic Resource, Nepro, and Ensure but for the virtual patient's simulation, the study only considered Glucerna. In addition, the daily nutrition intake for a critically ill patient is based on the specific goal feed, GF (kcal) recommended by ESPEN [24] that can be determine based on the body weight. If indirect calorimetry is not available, the use of the 25kCal/kg/day for daily calorie intake for a patient is adequate. For example a 60kg patient needs 1500kCal/day to be consumed in a day (i.e. 60kg x 25kCal/kg/day = 1500kCal/day). The glucose content in Glucerna is 0.0872 g/mL for each 1 kCal/mL. Thus, a 60 Kg patient require approximately 5.08g (or 121.9g) of glucose in an hour which can be calculated as shown in equation (8).

$$\frac{1500kCal/day}{24\,hr/day} \div (1\,kCal/mL) = 62.5\ mL/hr\ \times\ (0.0812\ g/mL) = 5.08\ g/hr\ of\ glucose \qquad (8)$$

Table 1. Patient demographics.

	HTAA cohort	
Total patients	92	
Weight (mean)	67.7kg	
Age (years - mean)	50 years old	
% Male	59.8%	
With Comorbidity	45.7%	
Mortality	41.3%	
Length of Stay (mean)	4.6 days	
	Num. patients	%
Medical	53	58%
Surgical	28	30%
Gastrointestinal	1	1%
Neurological	10	11%

Table 2. Nutrition information used in HTAA.

Nutrition	kCal/mL	Glucose content (g/mL)
Glucerna	1	0.0812
Jevity	1.5	0.216
Diabetic Resource	1	0.0872
Nepro	1.8	0.0863
Ensure	1	0.097

**Full product information can be obtained from the Abbott & Nestle websites respectively.*

2.3 Stochastic model

STAR protocol using stochastic forecasting which provides a control framework for future outcomes mainly to mitigate hypoglycaemia cases. This protocol minimise risk of hypoglycaemia cases (5% for BG < 4.44 mmol/L, ≈ 1% for BG < 4.0 mmol/L).

Current SI parameter from ICING model will be identified once a BG measurement is entered, and a range of SI values (used for future prediction) is generated using a stochastic model. The range of predicted SI is then used together with the ICING model to generate BG results and most suitable therapy correlate with potential insulin and nutrition administration combinations. The result outcomes balance clinical assignment, nutrition rates, and BG variability. Using the range of SI generated previously, simulation of a range of BG outcomes begins. For every tolerable insulin rate, the BG outcomes are simulated between the 5th percentile (refer to Figure 2, points A-C) and 95th percentile (refer to Figure 2, points D-F) [18, 19].

If BG outcome is below the targeted range (5th - 95th percentile), the combination of insulin and nutrition administration is discarded and the simulation of algorithm moves on. Otherwise, if the outcomes are within the tolerance range, the combination is saved [18]. Eventually, if the prediction closer to the lower limit than any previous combinations, it is saved as a possible treatment.

The skewed nature of the BG results distribution makes the 5th percentile target is prioritized for control. As shown in Figure 2, it ensures BG level to be in the desired target range of the 4.44 - 8 mmol/L that specifically reduced the acuteness of organ failure. 95th percentile target ensures the tightness of glycaemic control which limits the possibility of mild hyperglycaemia event. [18, 19].

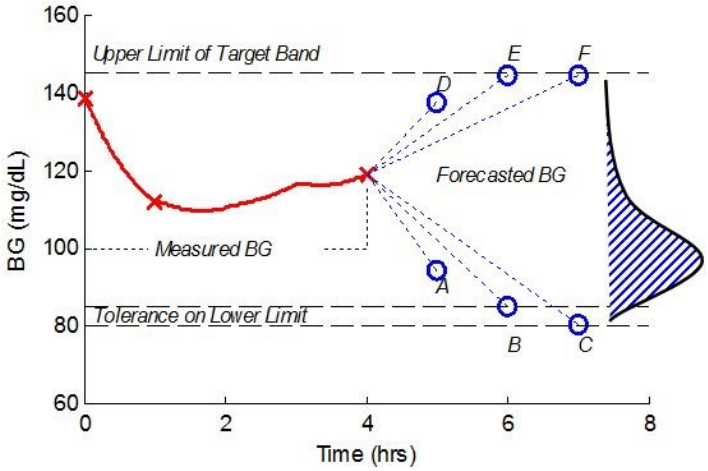

Figure 2. The generated BG forecast (points A to F) within the target 5th-95th percentiles: 80-145 mg/dL (i.e. 4.44-8.0 mmol/L) [19].

2.4 Virtual trials

Before clinical testing (Figure 3) is commenced, in-silico virtual trials should be conducted to prove the study performance and to ensure the patient's safety. The virtual trial simulations will be compared to the raw clinical data obtained from the ICU chart to validate the outcomes to observe the improvement on the improvised blood glucose management by using STAR with controlled goal feed. In addition, the performance of STAR with controlled goal feed and without GF will be compared and analysed.

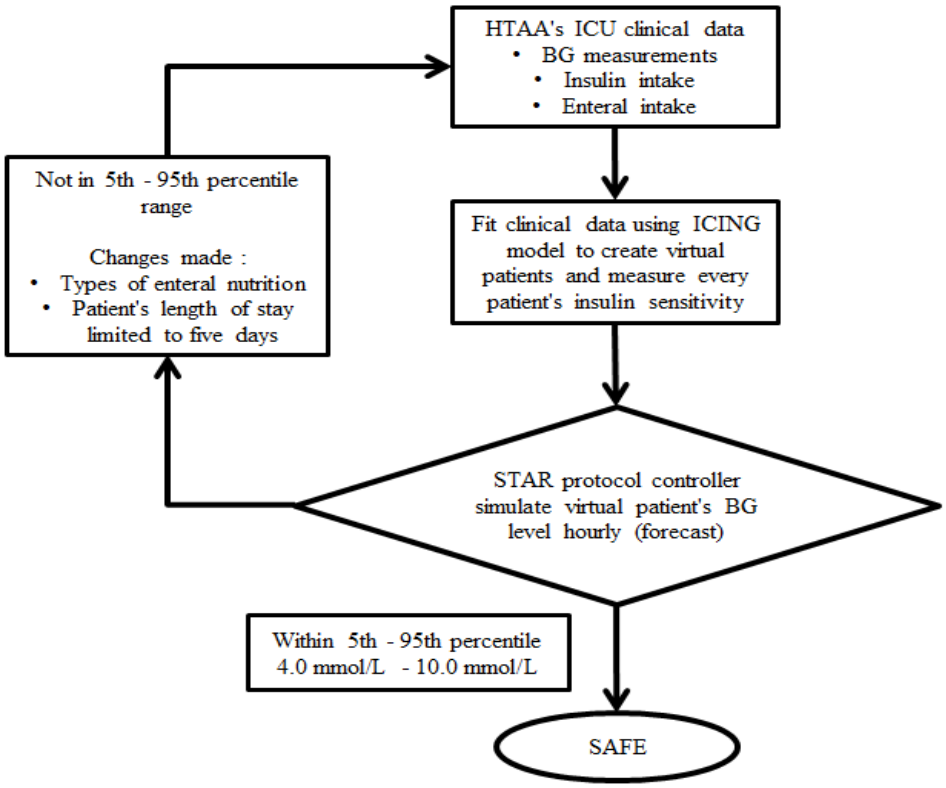

Figure 3. Virtual trial simulations procedure.

2.5 Performance metrics

Performance of STAR virtual trial simulations is classified within the percentage of BG level that must be in the targeted range. Clinical labour performance will be assessed by the frequency of BG measurements and the patient's safety will be assessed based on the level of hypoglycaemia event; severe = (BG < 2.2mmol/L), mild = (BG < 4.0mmol/L).

3. Results and discussion

3.1 Performance of STAR protocol

Based on the insulin-glucose rates tabulated in Table 2, it shows that STAR with controlled GF (5.7 – 8.7 mmol/L) offers tight and safe glycaemic control that helps to reduce hypoglycaemia and hyperglycaemia incidences in the ICU. It is also proven by prior study by [12, 13, 16, 18, 20]. For instance, the amount of exogenous insulin administrated of STAR with controlled GF is less compared to the other two virtual trial simulations, which leads to low (four cases in STAR-GF and eight cases for the other two) severe hypoglycaemia incidences. In fact, the glucose rate in STAR with controlled GF has the highest amount of glucose of 5.8 g/hour, which approximately close to the calculated nutritional goal feed of 5.08 g/hr as explained earlier in section 2.2.

Table 3. The overall performance of STAR without and with controlled GF.

Whole cohort statistics	STAR Original	STAR Glucerna	STAR Glucerna_GF
# patients:	92	92	92
Total hours:	11594	11594	9964
# BG measurements:	**7038**	**6875**	**5384**
BG median	7.4	7.3	7.1
[IQR] (mmol/L):	**[6.0 - 9.2]**	**[5.9 - 9.1]**	**[5.7 - 8.7]**
Desired glycemic bands:			
% BG in 6.0-10.0mmol/L	57.6	57.2	56.8
% BG in 4.0-5.9mmol/L	21.9	23.5	26.3
Hyperglycemic bands:			
% BG > 10.0mmol/L	**17.7**	**16.5**	**13.6**
Safety glycemic bands:			
% BG < 4.0mmol/L	2.8	2.8	3.3
# patients < 2.2mmol/L	**8**	**8**	**3**
Interventions:			
Median insulin rate	5	4.5	4
[IQR] (U/hr):	[2.0 - 8.0]	[2.0 - 8.0]	[2.0 - 7.5]
Median glucose rate	3.9	4.5	**5.8**
[IQR] (g/hour):	[1.9 - 6.6]	[1.9 - 6.6]	[3.9 - 6.6]
Median glucose rate	60%	70%	89%
[IQR] (% goal):	[30-100]	[30-100]	[60-100]

3.2 Safety

Simulation of STAR based on HTAA clinical data ensures the patient's safety in reducing hypoglycemia cases especially patient with controlled GF. Prior study [6, 14] proven that ≈ 1% of hypoglycemia case reported when STAR is introduced. However, there are three patients (≈ 3%) will be experiencing hypoglycaemia. Although the chance of getting hypoglycaemia is slightly higher in Malaysia ICU this is due to the level of comorbidities experienced by Malaysian patients by referring to Table 1 about 45.7% patients associated with comorbidities, which are far more severe, compared to the other countries that used STAR [6, 18].

In terms of mortality, the IIT protocol implementation at the HTAA ICU has reported high mortality rate of 38 cases (41.3%). However, the prior studies on the STAR implementation in several hospitals in Christchurch, NZ and Gyula, Hungary indicated low mortality rate of 6.4% (Christchurch) and 0% (Gyula) [6, 19]. Thus, this outcome proves that STAR is effectively safe to be implemented in Malaysia ICU as it can reduce the mortality rates significantly.

3.3 Clinical effort

Table 2 shows a decreasing number of total hours and blood glucose measurement which is the actual time for the nurses have to spend at the patients' bedside. The significant changes occur in terms of total BG measurements taken is reducing from 7038 to 5384. In fact, the total hour's patient will undergo therapy in reducing and maintaining their blood glucose levels within targeted band is reduced significant by 1630 hours. Based on prior study, STAR reduces the measurements per day by 7%, which decrease nurse's workload and clinical burden [14, 15, 25].

Previously with IIT protocol, HTAA patients are given more than five types of nutrition based on their comorbidities. Each type of nutrition as listed in 2.2 has a different amount of glucose content. The reason of using different types of nutrition is to tolerate with the patient's comorbidities in order to

minimize the risk of getting worse, for example, a patient with acute kidney injury (AKI) required only 1.4 – 1.8g/kg/day [26] of protein intake. Thus, each type of nutrition is formulated based on the targeted group. However, only Glucerna is considered in this study as to standardize the STAR protocol with the minimum glucose requirement for all patients. This is done by neglecting the types of nutrition that patients supposed to take based on their comorbidities. Surprisingly, the performance of STAR with controlled GF that used only Glucerna as nutrition input is significantly improved compare to the other two trials underwent STAR in terms of reducing hypoglycaemia and the total of BG measurements take as explained earlier.

In addition, the introduction of controlled GF which is taken into account the amount of nutrition (i.e. the glucose content) required by the patient and the patient's body weight (refer to 2.2) This goal feed is necessary to be determined before STAR is commenced to ensure that patient will feed well and fully recovered during their stay in the ICU. In addition, the aim of controlled goal feed is to avoid the significant weight loss due to deficient amount of nutrition given to the patient. However, excessive glucose in the blood will lead to hyperglycemia incident meanwhile insufficient amount of nutrition will cause hypoglycaemia. Thus, it is the best practice for the physicians to determine the patient-specific GF before starting any treatment to the patients to avoid any mishaps that would give harm to the patient.

4. Conclusions

The performance of STAR shows significant reduction of 23% on the total BG measurements taken which consequently reduced the clinical burden. The protocol also has reduced the hypoglycaemia events to only 3 patients once STAR is introduced with controlled goal feed based on patient-specific. Thus, by implementing STAR protocol in the Malaysia ICU will help nurses and physicians in controlling BG levels in the chaotic ICU setting as STAR protocol is proven safe to all critically ill patients with or without comorbidities. However, the study is limited to only one general hospital in assuming that the other Malaysia general hospital follows the standard IIT protocol. In fact, the patient races: Malay, Chinese and Indian, and other demographics factors that might arise in the other general hospital are not considered in the study that might affect the outcomes of the study. Thus, a larger cohort from other general hospitals from different states, which considered every demographic and comorbidity aspects should be considered in the future study to validate the results obtained in this study.

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