Efficacy and Safety of SPRINT and STAR Protocol on Malaysian Critically-Ill Patients

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***Abstract*—Intensive care unit patients may have a better glycaemic management with the right control protocol. Results of virtual trial performance on Malaysian critically-ill patients adopting a model-derived and model-based control protocol known as SPRINT and STAR are presented in this paper. These ICU patients have been treated by intensive sliding-scale insulin infusion. The effectiveness and safety of glycaemic control are then analysed. Results showed that patient safety improved by 83% with SPRINT and STAR protocol as the number of hypoglycaemic patients significantly reduced (BG<2.2 mmol/L). Percentage of time within desired bands and median BG improves in both SPRINT and STAR. However, the improvements are associated with higher number of BG measurements (workload).**

Keywords—model-based protocol; hyperglycaemia; ICU patients.

I. INTRODUCTION

Stress-induced hyperglycemia is prevalent in the intensive care unit (ICU), occurring in patients even without prior diabetes [1]–[3]. Hyperglycaemia worsens outcomes, namely increasing the risk of severe infection, myocardial infarction, multiple organ failure and at worst, mortality [1]. Many studies [4], [5] demonstrated that tight glucose control (TGC) may lessen ICU patients' mortality and other negative outcomes. A lot of TGC studies, either successful or unsuccessful had adopted nurse-implemented protocol that comes with some disadvantages: to name a few, as protocols are not individualized it is more of a one-size fits all method, some protocols may be ad-hoc or based on experience. Furthermore, providing round the clock care for ICU patients while adopting TGC has proven to be taxing.

One approach to develop a glycaemic control protocol that can be implemented within ICU is through model-based method. Model-based protocols deliver patient specific control where the control protocol can be devised individually. Through model-based methods, virtual trials may be simulated to design or develop protocols in-silico. Herewith attention to control glycaemia either through feed and/or insulin (subcutaneous, IV, bolus) 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.

SPRINT [4], a model-derived protocol was first implemented in Christchurch Hospital Department of Intensive Care in August 2005 and has treated over 1500 patients. SPRINT protocol has been effective at decreasing organ failure and mortality [6], [7] giving the most secure control over all patients of several extensive studies [8], [9]. It modulates both nutrition and insulin to provide tight glycaemic control. Insulin and dietary inputs are taken into account on hourly or 2-hourly blood glucose (BG) measurements for TGC. The protocol specifies carbohydrate intake, formula and/or goal feed rates [10], [11]. SPRINT is a paper-based protocol, developed through extensive computer simulations and does not require a bed-side computer.

Stochastic Targeted protocol (STAR) [12], downloadable on a tablet is a model-based protocol that uses a clinically validated glucose-insulin model which provides patient specific recommendations of insulin and nutrition while ensuring a 5% maximum risk of hypoglycaemia. STAR can be adopted over a scope of clinical scenarios and used for real-time bedside care. The adaptability of STAR includes to local nutrition practices, desired BG target levels,

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TABLE 1 SOCIO-DEMOGRAPHIC CHARACTERISTICS

Socio - Demographic Characteristics	Total N = 91
Gender	
Female	42
Male	49
Mortality	
Unknown	3
Dead	35
Alive	53
Admission Category	
Surgical	28
Medical	63
Age groups (years)	
< 29	10
30-39	10
40-49	14
> 50	57
Ethnicity	
Indian	2
Others	3
Chinese	5
Malays	81

measurement frequency and patient safety within a predefined risk management approach [12], [13]. Since 2011, 2 ICUs have used STAR as the standard of care, namely Christchurch Hospital ICU, New Zealand and Kalman Pandy Hospital ICU, Guyla, Hungary.

This study aims to assess, evaluate and compare the current clinical practice in a Malaysian ICU setting, Hospital Tengku Ampuan Afzan (HTAA) against SPRINT and STAR protocol performance using Malaysian critically-ill data. Both SPRINT and STAR protocols have managed to achieved BG band within 4.4-8.0 mmol/L at 93% and 86.6% respectively in clinical trials [12]. It would be interesting to see how Malaysian ICU patient that has been treated with intensive sliding-scale insulin infusion therapy fares against model-based/model-derived protocol. Assessment and comparison of protocols are done through virtual trials, focusing on efficiency, safety and overall glycaemic control. Virtual trials provide the requirement to design the protocol in-silico by testing on virtual patient (actual patient data) to optimize protocol performance and safety without risk on actual patient. The simulation results would provide a basis of guideline if HTAA ICU would opt for a model-based/derived control protocol in future [14].

II. METHODS

A. Patients Data

Virtual trials were performed on retrospective data of 91 critically ill patients treated under intensive sliding-scale insulin infusion at the ICU of HTAA. The socio-demographic characteristics and cohort details are summarized in Table 1. Malay ethnicity makes the largest cohort at 89% and percentage of male patients is 54%. 69% of patients are under medical category and 63% of patients fall under age cohort of over 50 years old. The intensive insulin protocol used in HTAA to maintain BG concentration target was set at 5.1-8.0 mmol/L. The study was registered under the National Medical Research Register (NMR-13-1592-18706). Ethics was granted by IIUM Research Ethics Committee and National Institute of Health (NIH).

B. HTAA Sliding Scale Protocol

The flowchart in Figure 1 shows the intensive insulin infusion protocol adopted in the ICU of HTAA. BG target is between 5.1 mmol/L – 8.0 mmol/L. Monitoring of BG is done hourly once insulin is administered and when there is no requirement of insulin rate change for 2 consecutive hours, BG is then measured 2 hourly. Frequency of monitoring is less once patient is considered stable. For detailed description of the protocol, refer to Figure 1.

C. System Model

The glucose-insulin physiological model utilized as a part of this study is clinically-validated [15]. Known as ICING [15] model, it utilizes past and current BG values, past nutrition past insulin measurements to register the insulin sensitivity, *SI* of the patient over the previous time period, based on parameter identification algorithm [16] which fits the model to the clinically observed behavior.

D. SPRINT Protocol

SPRINT [6] protocol was implemented as a clinical practice change in intensive care unit of Christchurch Hospital in 2005. The entry criterion for the SPRINT protocol was a BG measurement of greater than 8 mmol/L on normal patient where 8 mmol/L represents higher glycaemic level. The BG measurement was taken hourly to ensure tight control and once patient is stable, two-hourly measurement is used. SPRINT will stop once patient is adequately self-regulating and stable for 6 or more hours with over 80% of the target feed [10], [11]. SPRINT has a lower and tighter BG target at 4.4-6.1 mmol/L.

E. STAR Protocol

The STAR (Stochastic Targeted) [12], glycaemic control protocol, has been used in Christchurch Hospital ICU since June 2011 [12]. Starting criteria for STAR is two continuous BG measurements over 8 mmol/L within a 4-hr period. The BG target range of STAR is 4.4 -8.0 mmol/L. This protocol utilizes a physiological glucose-insulin framework combined with stochastic models of *SI* inconstancy [17], [18] to decide the most fitting insulin and nutrition treatment combination. *SI* is an important indicator in clinical blood glucose (BG) control as it demonstrate the overall glycaemic reaction of a body to exogenous insulin and nutrition inputs.

This measure of glycaemic reaction to exogenous sources of info is especially important for STAR which expects to minimize the danger of hypoglycaemia by straightforwardly representing likely fluctuation of *SI*.

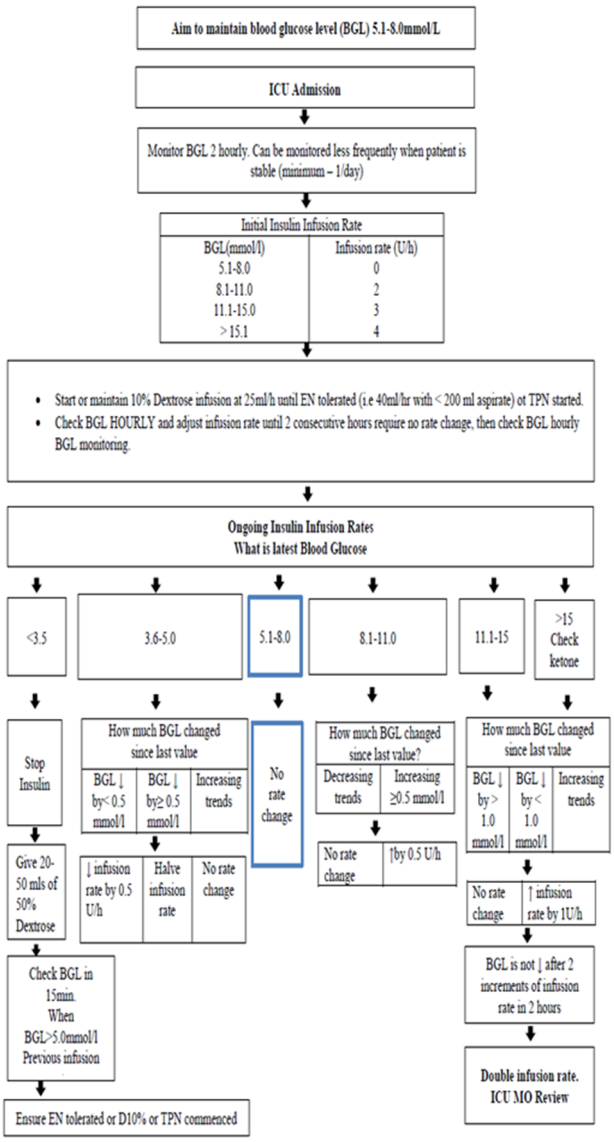

Fig 1. HTAA Intensive Insulin Protocol

F. Virtual Trials

Virtual trials have played an important part in tight glycemic control by providing safe and efficient way to analyze, develop or validate glycemic controls protocol. Figure 2 shows the steps of virtual trials starting from fitting, followed by simulation. The resulting time-varying *SI* profiles represent time-varying metabolic status for individual patients. This profile can be used to simulate the BG level for different insulin and dextrose inputs, associated with different control protocols. Thus, virtual trials present the closest view of possible behaviors seen typically in clinical setting.

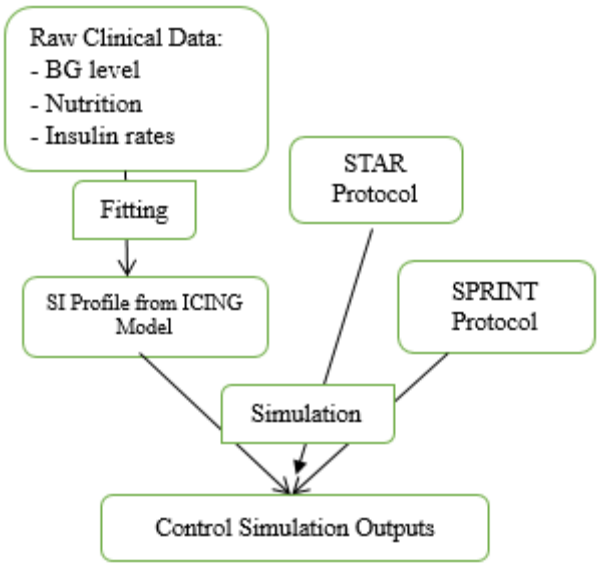

Fig.2: Virtual trial process

G. Analysis

The efficacy of SPRINT and STAR protocol on HTAA ICU patients is assessed in terms of performance and safety. A statistical Mann-Whitney U test was also done where a p-value < 0.05 was considered to be significant.

Metrics compared:

- Performance: Percentage of time in BG band (4.0-6.1 mmol/L, 4.4.-7.0 mmol/L, 4.4-8.0 mmol/L and 8.0-10 mmol/L). Median and interquartile (IQR) of BG levels.
- Safety : Number of patients with moderate hypoglycaemia (BG< 4.4 mmol/L)
- Safety : Number of patients with severe hypoglycaemia (BG< 2.2 mmol/L)

III. RESULTS

Table 2 presents the virtual trial results of glycaemic control performance between HTAA (actual clinical data), SPRINT protocol and STAR protocol.

Figure 3 until Figure 5 illustrate the per-patient cumulative distribution functions (CDFs) of BG levels from actual clinical data of HTAA ICU and the performance of SPRINT protocol and STAR protocol, respectively. From Figure 3, Figure 4 and Figure 5 it can be seen that control of BG are tightest with STAR protocol. Outliers in Figure 3 can be seen, representing patients whom are not effectively controlled with BGs recorded at over 30 mmol/L. In SPRINT

protocol, these outliers are tighter and in Figure 5 under STAR protocol, the CDF of BG is smoother with 95th percentile of patients recorded BG lesser than 11 mmol/L.

TABLE.2 VIRTUAL TRIALS OF STAR PROTOCOL AND SPRINT PROTOCOL IN COMPARISON TO CLINICAL DATA UNDER SLIDING-SCALE PROTOCOL AS PRACTICED IN HTAA ICU.

Whole cohort statistics	HTAA Clinical Data	SPRINT Protocol	STAR Protocol	p-value
Total hours:	11362 hours	11194 hours	11209 hours	> 0.05
Num BG measurements:	5509	8030	7373	< 0.05
BG median [IQR] (mmol/L):	8.1 [6.4 - 10.3]	7.7 [6.2 - 9.9]	7.8 [6.2 - 9.6]	<0.05
% BG within 4.0 - 6.1 mmol/L	17.68	23.77	22.92	<0.05
% BG within 4.4 - 7.0 mmol/L	29.66	38.18	35.70	<0.05
% BG within 4.4 - 8.0 mmol/L	45.16	52.00	51.95	<0.05
% BG within 8.0 - 10.0 mmol/L	24.65	24.06	27.30	> 0.05
% BG > 10.0 mmol/L	27.94	23.30	19.76	<0.05
% BG < 4.4 mmol/L	4.47	1.97	2.59	<0.05
% BG < 4.0 mmol/L	2.60	0.91	1.46	<0.05
% BG < 2.22 mmol/L	0.1634	0.0126	0.0135	<0.05
Num patients < 2.22 mmol/L	6	1	1	<0.05
Median insulin rate [IQR] (U/hr):	2.0 [0.5 - 3.0]	4.0 [3.0 - 5.0]	6.0 [3.0 - 8.0]	<0.05
Median glucose rate [IQR] (g/hour):	4.1 [2.6 - 6.1]	2.0 [2.0 - 3.3]	3.6 [1.9 - 5.8]	<0.05
Insulin Sensitivity median [IQR] (L/mU.min)	0.000159 [0.000119 – 0.000228]			

IV. Discussions

Percentage of BG time band within 4.4-8.0 mmol/L is almost the same for SPRINT and STAR protocol at 52% and 51.95% as compared to HTAA at 45.16%. Generally, the overall performance is similar although higher percentage is obtained in SPRINT and STAR protocol. The trend is similar across other time band (4.0-6.1 mmol/L and 4.4 -7.0 mmol/L) where SPRINT protocol has the highest percentage. This result differs from what has been achieved by SPRINT and STAR in other clinical trials where over 86% of the time BG is within the desired time band (4.4-8.0 mmol/L) [12].

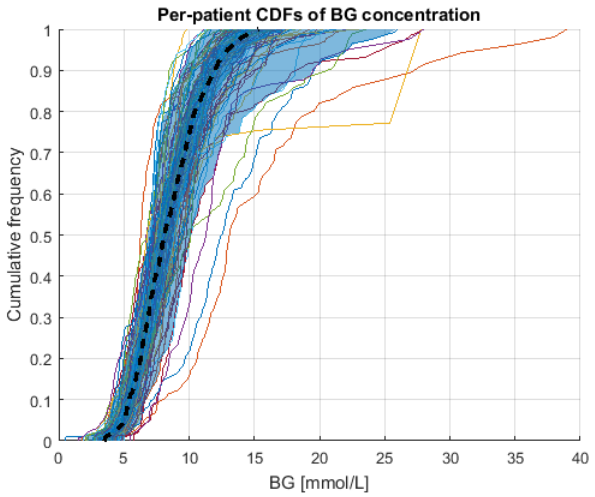

Fig 3 Cumulative distribution frequency (CDF) for Clinical data

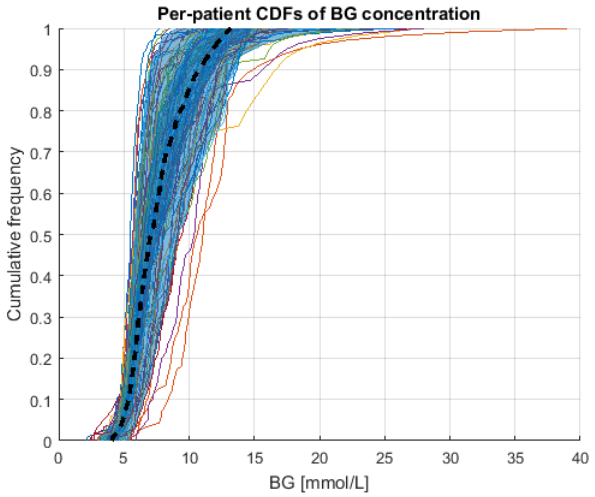

Fig 4 Cumulative distribution frequency for SPRINT Protocol

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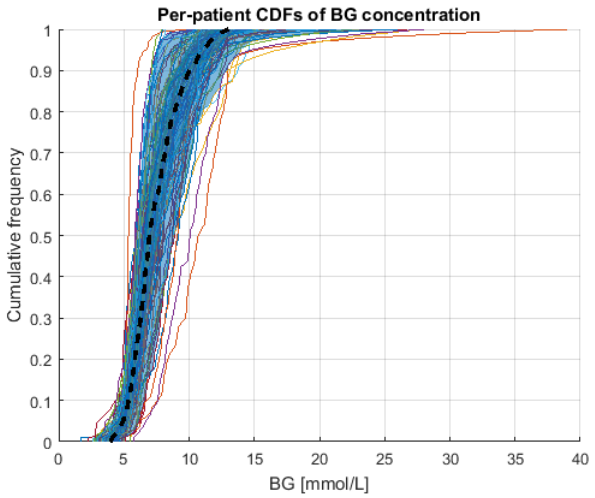

Fig 5 Cumulative distribution frequency for STAR Protocol

The explanation for this might lies under the cohort characteristics differences, particularly the SI. Figure 6 illustrates the CDF of SI for Malaysian ICU against SPRINT ICU patients. It can be seen here that the SI of Malaysian patients are lower. SI is central model parameter of interest as response to insulin can change dramatically between patients. A closer look is needed to analyze the clinical conditions that might be associated with lower SI. In HTAA, 69% of the patients are treated due to medical conditions which explain the lower SI.

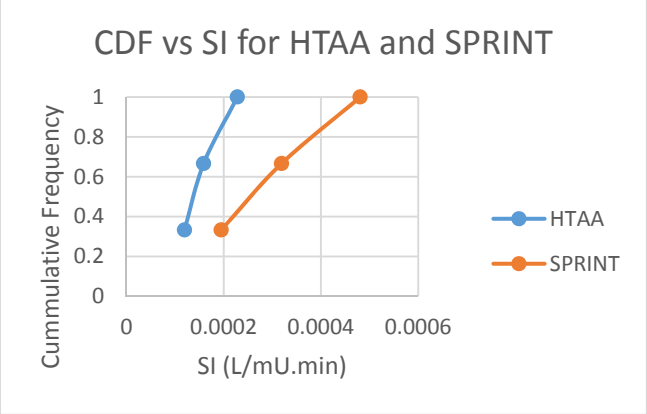

Fig 6 Cumulative distribution frequency versus Insulin sensitivity for HTAA and SPRINT Protocol

In Figure 7, it is illustrated that the distribution of SI over the 2 cohorts are significantly different. It is clear that SPRINT patients has a wider and flatter SI distribution. Patients in SPRINT has greater inter-patient variability whereas HTAA has less variability of SI. But even so, both SPRINT and STAR protocols with proven results in attaining higher BG median, higher percentage time in desired band, couldn't obtain the same level of percentage through virtual trials.

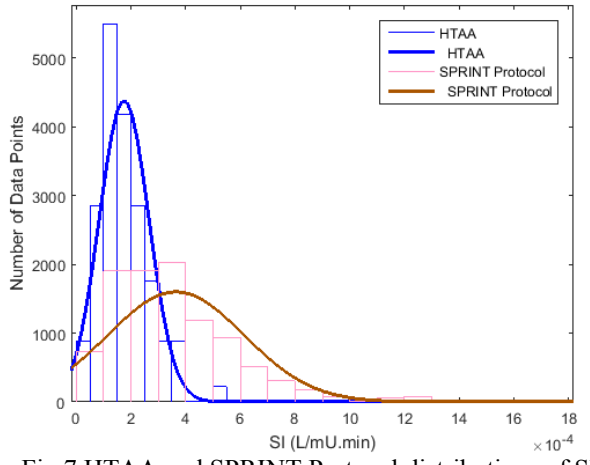

Fig 7 HTAA and SPRINT Protocol distributions of SI.

Better glycaemic outcomes in terms of patients safety is clearly achieved in STAR protocol where percentage of BG>10 mmol/L is reduced by 29.3%. SPRINT protocol on the other hand reduced 16.6% of BG> 10 mmol/L. Higher percentage in reduction of mild hypoglycaemia is demonstrated by SPRINT protocol (BG<4.4 mmol/L) by 56% and STAR by 42%. Both SPRINT and STAR only had 1 patient with severe hypoglycaemia (BG<2.2 mmol/L), an 83% improvement. This supports the capability of SPRINT and STAR that firmly controls glycaemia particularly patients who are in danger of hypoglycaemia.

Control efficiency is associated with higher insulin inputs, and evident here as STAR protocol has the highest insulin rate at 6 U/hr, which is 4 Units higher than HTAA. Feeding is lower with 3.6 g/hr in STAR, 2 g/hr in SPRINT and 4.1 g/hr in HTAA. These results show that feed reduction is related to better glycaemic levels. Glycaemic control might be difficult to achieve with higher feeding rate but nutrition rules used in STAR still corresponds to 100% ACCP guidelines.

The key point seen here in these virtual trial results lies with the capacity of SPRINT and STAR in providing safe glycemic control is often challenging within ICU patients. This is something that is unique to model-based protocol as has been demonstrated and achieved by STAR protocol.

However there are many other area and issues that will be worthy to look at. For example, clinical integration that requires compliance of staff, differences in patient cohort (surgical, medical, cardio), diabetic status, differences in feed target practice etc. All these points when put into consideration might bring us to a different explanation to the virtual trials presented in this paper.

V. Conclusions

This study presented an analysis of clinical practice from an ICU in HTAA, simulated with SPRINT and STAR protocols. Through virtual simulations, patient's safety has been improved by 83% where only 1 patient had a severe case of hypoglycaemia. Overall, both SPRINT and STAR protocols have shown the ability in providing a safe and effective treatment. Thus, a model-based approach can safely be adopted and introduced into a Malaysian ICU settings

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