# Virtual Trial Protocol Analysis of Nursing Workload Intensity within ICU

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*Abstract*— **Currently, effective glycaemic control protocols consume significant nursing time, which may be unsustainable as the number of patients requiring control increases with increasing rates of diabetes. This paper investigates the safety and efficacy of basal insulin therapy as a means to reduce nurse workload associated with glycaemic control in intensive care patients with stress hyperglycaemia. Validated virtual trial simulations (N = 40 patients) of a successful glycaemic control protocol (SPRINT) using 1-2 hourly interventions and a modified version using 4 hour interventions augmented with basal insulin therapy using Glargine. An additional model was used to capture the kinetics of Glargine. Workload was assessed by counting the total number of interventions (BG measurements, changes to insulin and nutrition rates) per day. Glycaemic performance was assessed by time in the target band (4.4-7.0 mmol/L) and number of severe hypoglycaemic episodes (BG<2.2 mmol/L). Workload reduction is around 30% (p<0.001) due to basal insulin therapy. Glycaemic control performance was slightly reduced from 86% to 80% (p=0.006) time in the target band using basal insulin therapy and 4 hourly interventions. However, safety was maintained with 0 incidence hypoglycaemia. Basal insulin therapy enables glycaemic control protocols with reduced intervention frequency while maintaining performance and safety. Reduced intervention frequency directly translates into reduced nurse workload associated with glycaemic control.**

*Keywords*— **Nursing effort, Glycaemic control, Model-based Protocol, Glargine.**

## I. INTRODUCTION

Stress-induced hyperglycaemia is relatively common in the critically ill and may occur in patients without any prior history of diabetes [1-3]. Studies have shown that controlling glycaemia to normal levels can reduce mortality and morbidity in the intensive care unit (ICU) [4-6]. With the prevalence of diabetes increasing rapidly [7], the clinical burden of implementing glycaemic control in the ICU could become unsustainable with current methods.

Successful tight glycaemic control (TGC) protocols for critical care have typically relied on average blood glucose (BG) measurement intervals of 1-2 hours, to avoid the risk of hypoglycaemia [6,8]. However, measurements and interventions at this frequency can consume significant nurse workload [9-11]. Gartemann et al. reported that TGC activities consumed 7.1% (42 mins) of nurse work time during a 12-hour shift [10]. With an increasing number of patients entering the ICU with impaired glucose tolerance, strategies to reduce the nurse workload associated with TGC are essential.

One potential method for reducing nurse workload associated with glycaemic control is to treat ICU patients with hyperglycaemia more like ambulatory diabetics and use basal insulin therapy. Our hypothesis is that with long-acting basal insulin, patient glycaemia will be more stable and require fewer changes to infused insulin rates and enteral/parenteral nutrition rate. The validity of this hypothesis can be effectively tested and potential protocols refined in simulation prior to a clinical pilot trial.

This paper presents an *in-silico* proof of concept study investigating the efficacy and safety of basal insulin therapy with Glargine for reducing nurse workload associated with glycaemic control. Simulations are conducted using a validated virtual trial method [12,13] coupled with a 4-compartment model of Glargine [14] to accurately capture the insulin kinetics. The paper-based SPRINT glycaemic control protocol [4] is tested, where 4-hourly interventions are used in conjunction with basal insulin therapy, rather than the standard 1-2 hours.

## II. METHODOLOGY

The virtual trial method used in this study relies on a physiological model of the glucose-insulin system and real patient data. The model used for this study is that of Lin et al. [15]. For simulation of the behaviour of subcutaneous insulin, an additional model is required and the model of Wong et al. [14] is used.

Retrospective data from 40 patients in ICU from Intensive Care Unit, Christchurch Hospital totaling 8100 hours were used for this study. These patients all had more than 8 hours of 2U of insulin per hour and insulin sensitivity profiles with a low variability, to mimic the type of patient who might benefit from basal insulin therapy. Table 1 shows the median and interquartile range (IQR) of age, APACHE II score and length of stay (LOS). Patient cohorts were divided into three categories of LOS which were less than 5 days, 5 to 10 days and more than 10 days.



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Table 1 Patient Demographic

| Demographic | Median [IQR] |
|---|---|
| Patient (n) | 40 |
| Age (years old) | 59 [44 71] |
| Gender (female:male) | 19:21 |
| APACHE II score | 19 [17 27] |
| Length of stay (LOS) in days | 6 [4 11] |

The patient's time-varying insulin sensitivity metric (*SI*) was fitted to the actual clinical data using an integral fitting method [16]. 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.

The modified protocol called 4-Hour protocol was simulated and compared with actual clinical data of patients receiving intensive insulin therapy under SPRINT protocol. The frequency of BG measurements, changes in feed rates and intravenous (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. In 4-Hour protocol, instead of 2-hourly BG measurement when patient is stable, BG measurement frequency is reduced to 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. As SPRINT operates on the basis of estimating patient's apparent insulin sensitivity, the protocol is still applicable with a background infusion. Virtual trials are performed using updated SPRINT with daily dose of glargine.

In this newly simulated protocol, the dosing frequency of Glargine is once per 24 hours. The first dose is given 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.

Safety and performance of the protocols are evaluated by number of hypoglycaemic events (BG < 4.0 mmol/L), median and IQR of BG measurements level, percentage time spent in desired band (4.4-7.0 mmol/L), amount of insulin prescribed (IV boluses+Glargine), amount of nutrition given and nursing workload intensity based on number of interventions. Specifically, interventions that involved measuring BG levels, adjusting feed rates, administering SPRINT IV and Glargine bolus.

## III. RESULTS

Figure 1 shows a cumulative distribution frequency (CDF) comparison between two protocols. The 4-Hour protocol is indicated with solid line while SPRINT clinical with dashed line. Analysis by cohort depicts an almost similar performance in terms of BG control between the two protocols.

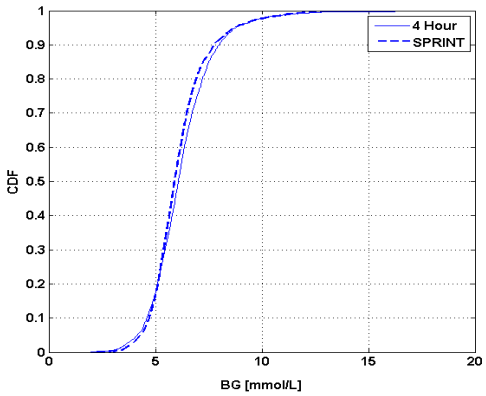



Fig. 1 Cumulative distribution function of BG measurement levels by cohort analysis for SPRINT clinical and 4-Hour protocol.

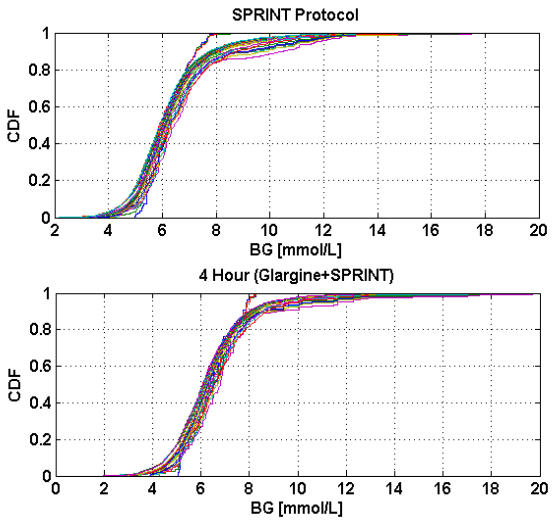



Fig. 2 Per Patient BG measurement levels of SPRINT Clinical and simulated 4-Hour protocol.

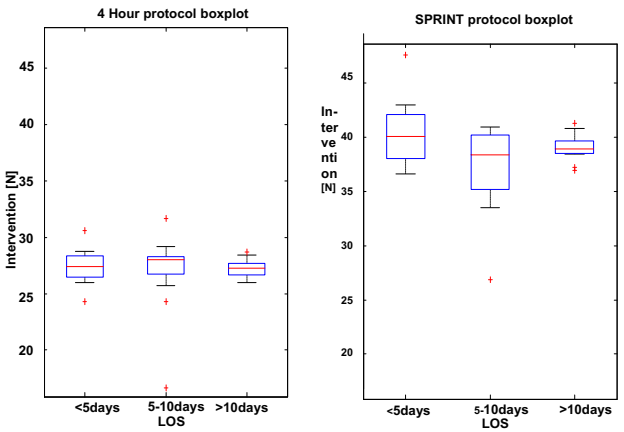
For a closer look at the effectiveness of protocols individually, Figure 2 depicts the per-patient BG measurements simulated for 4-Hour protocol and actual records from SPRINT clinical. Differences in tightness of control can be

seen between SPRINT clinical and 4-Hour protocol. SPRINT shows a tighter control with more than 80% of patients having BG measurement levels under 7.0mmol/L. This is closely followed by the 4-Hour protocol at around 70% patients with BG levels under 7.0mmol/L. More importantly, per-patient variability is not an issue with just a minimal number of outliers.

Table 2 shows median and [IQR] of BG [mmol/L], insulin sensitivity (SI) [mU.min/L], time band within 4.4-7.0 (mmol/L) [%], amount of insulin bolus (IV) [U/day], number of intervention [N/day] for nursing workload and feed (nutrition intake) daily [mmol/min] for SPRINT clinical and 4-Hour protocol. The p-value for each assessment is included in the table.

Table 2 Comparison of Simulated 4-Hour protocol and SPRINT Clinical.

| Median & IQR | SPRINT Clinical | 4-Hour Protocol | P-value (significant when <0.05) |
|---|---|---|---|
| BG [mmol/L] | 5.33 [4.96 5.67] | 5.39 [4.99 5.89] | p=0.035 |
| IV [U/day] | 46.47 [39.52 51.12] | 32.45 [28.77 40.87] | p<0.001 |
| Intervention [N] | 39.15 [37.14 40.74] | 27.25 [ 26.32 28.50] | p<0.001 |
| TimeBand [%] | 86.80 [77.99 91.57] | 80.77 [72.86 85.49] | p=0.006 |
| Feed [mmol/min] | 0.87 [0.87 1.09] | 0.87 [0.79 0.87] | Not significant |




(a) (b)

Fig. 3 Cohorts intervention boxplot (a) 4-Hour protocol (b) SPRINT Clinical

Figure 3 is the box plot and whisker comparison for the 4-Hour and SPRINT clinical. Number of interventions was compared to LOS less than 5 days, 5 to 10 days and more than 10 days. This is done to assess if there is a relationship between nursing effort and LOS.

## IV. Discussion

The virtual trial results of a combination and modified protocol referred to as 4-Hour protocol demonstrated a safe and promising protocol. An almost similar control both by cohort and per-patient analysis is achieved by the 4-Hour protocol as compared to SPRINT clinical. Significant clinical effort reduction is obtained with good performance in control quality and patient safety. Median BG measurement level, percentage within desired time-band (4.4-7.0mmol/L) and avoidance of hypoglycaemia achieved control as good as in SPRINT clinical. Feed rate in both protocols are similar with difference in upper and lower quartile. Interventions daily in SPRINT clinical are at 39.15 [37.14, 40.74] compared to 27.25[26.32, 28.50] in 4-Hour protocol. This reduction of around 12 daily interventions 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 [17]. Thus, a reduction of 12 units is roughly 60 minutes saved.

Results from Figure 3(a) of intervention box plot show that nursing effort once grouped per LOS is only slightly higher for LOS between 5-10 days. This might be attributed to the characteristics of Glargine build up that usually takes 3 days or longer before insulin is observed in plasma (Lehmann et.al., 2009). However, study is needed as to why less effort is required during the first 5 days. A different trend is recorded in SPRINT clinical where nursing effort is highest for LOS <5 days. Understandably, patients are much more dynamic at the start of ICU treatment. As reported by Carayon et al., patients with shorter LOS have slightly higher number of intervention [18].

Limitations to this study included number and criteria of patients simulated. Larger cohort would generate more statistics and enable thorough analysis. This virtual analysis only included 40 patients; therefore its results are a positive proof of concept and not conclusive. The insulin requirement of patients in this study is generally stable and consistent hourly which might contribute to the positive outcome.

In overall, this virtual trial results give a closer look at the potential benefits from Glargine as basal insulin therapy. More importantly, the outcome of the simulation opens a possible clinical proof of concept to demonstrate that reduction of nursing effort does not compromise patient safety and glycaemic control quality.

## V. CONCLUSION

This study successfully demonstrates a safe and effective approach in reducing nursing effort within an ICU setting while maintaining the benefits of tight glycaemic control.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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