The Effect of Glargine as Basal Insulin Support for Recovering Critically Ill and High Dependency Unit Patients: An In Silico Study

Jessica Lin*, Normy N Razak, Geoff Chase, **, Jason Wong**, Chris Pretty**, Jacquelyn D. Parente**, Aaron LeCompte, AJ**, Fatanah M. Suhaimi**, Geoff Shaw*, Christopher Hann**.**

*University of Otago Christchurch, Department of Medicine, Christhcurch, New Zealand (e-mail: jessica.lin@otago.ac.nz).
**University of Canterbury, Department of Mechanical Engineering, Centre of Bioengineering, New Zealand.

Abstract: Many critically ill patients are benefiting from extensive research done in tight glucose control (TGC) within the ICU. But moderate to high levels of hyperglycaemia are still tolerated within high dependency (HDU) and surgical units. The use and benefits of insulin protocols within these units have not yet been addressed in the literature**.** The management of tight glycaemic control still remains under the influence of ineffective standards characterized by tolerance for hyperglycaemia and a reluctance to use insulin intensively.

A validated Glargine and intravenous insulin-glucose pharmacodynamic model are presented. Virtual trial results on 16 stable ICU patients showed that Glargine can provide effective blood glucose management for these long term recovering patients. An initial intravenous injection and higher Glargine dosing is required for the first day to quickly lower elevated blood glucose levels. However, once patient's blood glucose levels are within a desirable range, Glargine alone can provide effective glycaemic management, thus reducing nursing effort. Median blood glucose for the entire cohort when simulated with the combination of Glargine and an intravenous insulin injection is 6.5 with interquartile range of [5.6, 7.5]. The 90% confidence interval is [4.6, 9.7] with no occurrence of hypoglycaemia. This in silico study provides a first virtual trial analysis of the in-hospital transition between intravenous and subcutaneous insulin for TGC.

Keywords: Glargine; High Dependency; Hyperglycaemia; Glucose Control; Basal Insulin Support.

1. INTRODUCTION

Stress-induced hyperglycaemia is prevalent in critical care and can occur in patients with no history of diabetes (Capes et al. 2000, Mizock et al. 2001, Van den Berghe et al. 2001). Critically ill patients exhibit increased endogenous glucose production, antogonised and erratic insulin production, and significantly increased insulin resistance. Hyperglycaemia worsens outcomes, increasing the risk of severe infection (Bistrian et al. 2001), myocardial infarction (McCowen et al. 2000) and critical illnesses such as polyneuropathy and multiple organ failure.

A number of studies have investigated the effects on patient outcomes when blood glucose levels are controlled with insulin, and revealed markedly positive results. The most notable is a study by Van den Berghe et al. (2001) who showed that tight glucose control averaging 6.1mmol/L reduced cardiac intensive care unit (ICU) patient mortality by 18-45%. The use of IV insulin therapy in ICU patients to correct hyperglycaemia, whether or not a patient is a diagnosed diabetic, became the focus of much discussion following this landmark study. Krinsley et al. (2004) showed a 17-29% reduction in mortality over a wider ICU population with a higher glucose average of 7.75mmol/L. Finally, the SPRINT protocol reduced mortality 36-47% with a more critically ill cohort (Chase et al. 2008).

While many ICU patients are benefiting from this research, moderate to high levels of hyperglycaemia are still tolerated within high dependency (HDU) and post-surgical units, such as the cardiac-thoracic care unit (CTCU). The use and benefits of insulin protocols within these units have not yet been widely addressed in the literature. (Whitehorn et al. 2006). The management of tight glycaemic control in these units remains under the influence of ineffective standard characterized by a tolerance for hyperglycaemia and a reluctance to use insulin intensively.

Based on current evidence from critically ill and surgical patients, it is logical to expect that maintenance of normoglycaemia within HDU patients would limit potential complications associated with elevated blood glucose levels. This assumption is not unreasonable as patients in the ICU and within HDU share an accelerated catabolic, hyperglycaemic state that also reduces the immune response. Extending tight control to these wards could minimise rebound hyperglycaemia on discharge to the wards (Goldberg et al. 2004) and minimise the development of (new) infections, thus improving overall patient care (Gubern et al. 2006).

HDU patients share more similarity in metabolic status to patients recovering from critical illness than to critical care patients in general. In Chase et al. (2008), as critically ill patients recover, their insulin sensitivity rises, but is still low compared to ambulatory Type 2 diabetic individuals (T2DM). Consequently, their insulin requirement decreases and the hourly doses are generally more consistent. In this study, insulin Glargine is investigated to see if it can effectively substitute intravenous insulin for these stable long term critically ill patients. Glargine is a long acting insulin, mostly used for basal insulin support in Type 1 diabetic patients. It is usually only used once to twice a day. If Glargine can be used effectively for stable ICU and HDU patients, nursing workload could significantly be decreased, which has added benefits. (Chase et al. 2008)

In this paper, a retrospective cohort of recovering, stable patients were selected from the SPRINT cohort (Chase et al. 2008). The effect of Glargine was simulated on these patients in virtual trials (Chase et al. 2007) to evaluate if Glargine can successfully substitute insulin boluses used in the SPRINT protocol for these patients. This paper uses an integrated pharmacodynamic model of insulin Glargine, intravenous insulin and glucose developed from Wong et al. (2008a,b,c,d) and Chase et al. (2005).

2. SYSTEM MODEL

The pharmacodymanic model used in this study integrates the Glargine compartmental model from Wong et al. (2008c,d) and the generic insulin-glucose model from Chase et al. (2005). The Glargine model has been validated against literature results (Wong et al. 2008c,d) and the model from et al. Chase (2005) has been clinically validated in TGC trials. The integrated model used in this study is defined:

Glargine Compartmental Model:

Precipitate State;

$$\dot{p}_{gla}(t) = \frac{-k_{prep,gla}\,p_{gla}(t)}{1 + k_{prep,gla} \Big/ r_{dis,\max}\,p_{gla}(t)} + u_{p,gla}(t) \tag{1}$$

Hexameric State:

$$\dot{x}_{h,gla}(t) = -(k_{1,gla} + k_d)\,x_{h,gla}(t) + k_{prepgla}\,p_{gla}(t)\frac{k_{prepgla}\,p_{gla}(t)}{1 + k_{prepgla} \Big/ r_{dis,\max}\,p_{gla}(t)} + u_{h,gla(t)} \tag{2}$$

Dimeric/ Monomeric State:

$$\dot{x}_{dm}(t) = -(k_2 + k_d)\,x_{dm}(t) + k_{1,gla}\,x_{h,gla}(t) + u_{m,gla}(t) \tag{3}$$

Interstitium:

$$\dot{x}_i(t) = -(k_3 + k_{d,i})\,x_i(t) + k_2\,x_{dm}(t) \tag{4}$$

where all variables in Equations (1)-(4) are defined:

$x_{h,gla}(t)$	Mass in glargine hexameric compt. [mU]
$p_{gla}(t)$	Mass in glargine precipitate compt. [mU]
$x_{dm}(t)$	Mass in dimer/monomer compartment [mU]
$x_i(t)$	Mass in the interstitium compartment [mU]
$r_{dis,max}$	Max glargine precip. dissolution rate [mU/min]
$u_{total,gla}(t)$	Insulin glargine input [mU/min]
$u_{p,gla}(t)$	Glargine precip. state insulin input [mU/min]
$u_{h,gla}(t)$	Glargine hexamer state insulin input [mU/min]
$u_{m,gla}(t)$	Glargine dimer/monomer state insulin input
$k_{prep,gla}$	Glargine precipitate dissolution rate [min^{-}1]
k_1	Hexamer dissociation rate [min^{-}1]
$k_{1,gla}$	Glargine hexamer dissociation rate [min^{-}1]
k_2	Dimeric/monomeric insulin transport rate into interstitium [min^{-1}]
k_3	Interstitium transport rate into plasma [min^{-}1]
$k_{d\,i}$	Rate of loss from interstitium [min^{-}1]
k_d	Rate of diffusive loss from hexameric and dimeric/monomeric state compartments [min^{-}1]

Insulin-Glucose Model:

$$\dot{I}(t) = \frac{-nI(t)}{1 + \alpha_I I(t)} + \frac{k_3 x_i(t)}{m_b V_i} + \frac{u_{ex}(t)}{V_i} \tag{5}$$

$$\dot{Q}(t) = -kQ(t) + kI(t) \tag{6}$$

$$\dot{P}1 = -d_1 P1 + D(t) \tag{7}$$

$$\dot{P}2 = -\min(d_2 P2; P\max) + d_1 P1 \tag{8}$$

$$P(t) = \min(d_2 P1, P\max) \tag{9}$$

$$\dot{G}(t) = -p_G G(t) - S_I G(t)\frac{Q(t)}{1 + \alpha_G Q(t)} + \frac{EGP - CNS + d_2 P2(t)}{V_G} \tag{10}$$

where all variables in Equations (5)-(10) are defined:

G	Total plasma glucose [mmol/L]
I	Plasma insulin [mmol/L]
Q	Interstitial insulin [mU/L]
EGP	Endogenous glucose production [mmol/min]
p_G	Glucose clearance [1/min]
CNS	Central nervous system uptake [mmol/min]
S_I	Insulin sensitivity [L/(mU.min)],
u_{ex}	Exogenous insulin input [mU/min]
D	Enteral dextrose infusion
$P1$	Represents stomach [mmol/min]
$P2$	Represents gut [mmol/min]
P	Glucose appearance [mmol/min]
n	Decay rate of insulin from plasma [1/min]
k	Effective life of insulin in the system
d_1, d_2	Transport rate [1/min]
m_b	Body Mass [kg]
α_G	Saturation of insulin-dependent glucose clearance [L/mU]
α_I	Saturation of plasma insulin disappearance [L/mU]
V_G	Glucose distribution volume [L]
V_I	Insulin distribution volume [L]

Figure 1 shows the Glargine compartment model structure by compartments. It is taken from Wong et al (2008c).

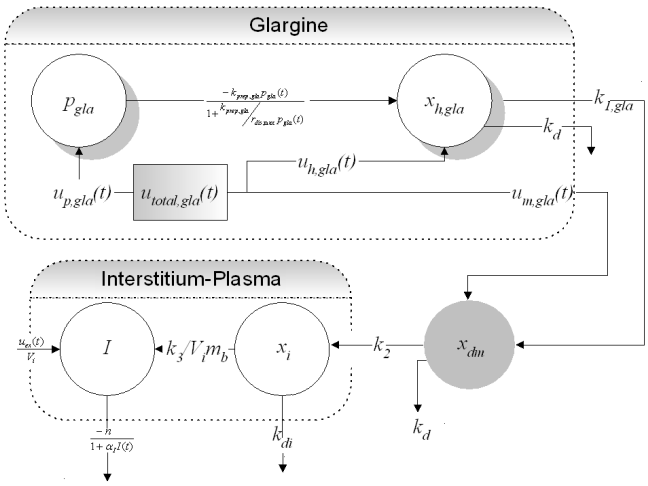

Figure 1. Structure of Glargine absorption kinetics model, starting from precipitate component p_{gla} it flows into dimeric/monomeric state x_{dm}, interstitium x_i and finally to plasma I compartment.

3. METHOD

3.1 Virtual Trial Patient cohort

The 16 patient cohorts used to create the virtual cohort for simulation covers a more stable portion of the general ICU population. These patient data are a small subset of the SPRINT (Chase et al. 2008) cohort. Patients were considered stable based on measurement frequency of 2 hours with no significant change in intervention or glucose, and thus cover only the latter portions of some patient stays. These patients are considered to represent a more stable patient group ready for transition to a less acute ward and subcutaneous insulin.

The APACHE II score (Median: 19, Range: 11-32), age, sex and mortality for the cohort are shown in Table 1. The average length of is 4.3 days (Range: 1.9-11.7 days). It is worth noting that the APACHE II scores have a much higher median and range than the larger cohorts in the glycaemic control research of Van den Berghe et al. (2001), Krinsley et al. (2004), but is more similar to Van den Berghe et al's more recent study (2006).

3.2 Virtual Trial Simulations

The patients time-varying insulin sensitivity (S_I) was fitted to the actual clinical data using an integral fitting method (Hann et al. 2005). Constraints are placed on S_I to ensure it is within a physiologically valid range. The resulting time-varying S_I profiles represent time-varying metabolic status for individual patients. Testing new interventions with this profile, in simulation, provides new outputs. Thus, the profile of S_I can be used to create "virtual patients" for testing insulin protocols. Using the known interventions tests the models prediction capability for model validation. In prior virtual trials, the results matched the clinical responses obtained when tested in the ICU (Lin et al. 2007, Chase et al. 2007).

Table 1. **Long-term virtual trial patient cohort**

Patient no.	*Medical Group*	*APACHE II score*	*Age*	*Sex*	*Mortality*
5004	Burns	11	43	F	N
5008	Resp. Failure	23	44	F	N
5020	Pancreatitis	19	68	M	N
5023	Unknown	NA	75	M	N
5028	Resp. Failure	15	67	M	N
5032	Pneumonia	31	70	M	N
5034	Pancreatitis	20	68	M	N
5050	Trauma	15	20	M	N
5058	Resp. Failure	18	75	M	N
5063	Pancreatitis	15	80	M	N
5070	Dissecting Aorta	20	76	F	N
5079	Unknown	NA	50	F	N
5092	Unknown	NA	76	M	N
5102	Sepsis	17	49	M	N
5111	Cardio. shock	29	58	M	N
5118	Haemorrhage	19	50	F	N
Median (range)		*19 (11-31)*	*57 (20-80)*		

In this study, the effect of Glargine was first tested where the sum of the clinical daily boluses for a patient is substituted by a single dose of Glargine. Further simulation was then carried out to test the effect of combining intravenous insulin injections with Glargine to aid the transition to subcutaneous insulin without losing glycaemic control. Virtual trial results were compared to the clinical SPRINT results to evaluate the performance of Glargine in place of intravenous insulin.

4. RESULTS

Simulation results from one patient are shown in Figure 2. The top panel shows the blood glucose through time. With Glargine only, blood glucose level for the first 50 hours is not well managed. This result occurs because the effective insulin takes a long time to build up to the same level achieved by using intravenous injections, as shown in the bottom panel. The middle panel shows the administration of insulin.

The simulated Glargine and intravenous insulin case uses a "priming" insulin injection in the beginning along with 5 times the specified insulin bolus of Glargine. This approach quickly builds up the effective insulin to a similar level as that achieved with intravenous insulin boluses only. The consequent blood glucose levels are similar to that achieved clinically, using intravenous insulin injections only. After the first day, the insulin requirement in Glargine is equivalent to that in intravenous insulin injections and is thus much lower.

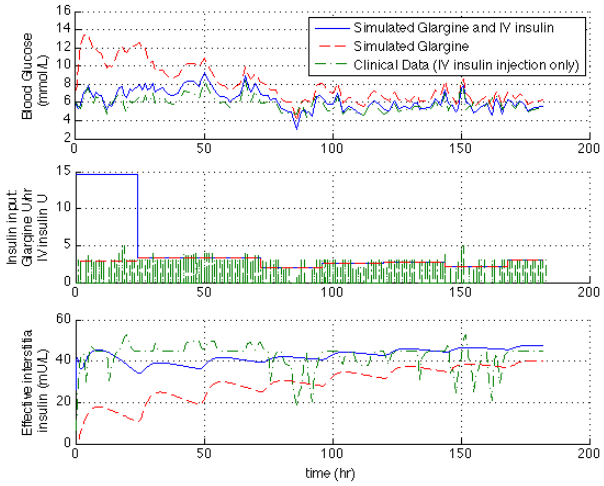

Figure 2. Simulation results from Patient 5008.

Figure 3 shows the responses of simulated Glargine with and without several different intravenous insulin boluses to raise the concentration of the effective interstitial insulin, Q. This analysis validated the choice of priming where it can be clearly observed how effective interstitial, Q has a different magnitude of build up depending on number of boluses and basal support.

The cohort blood glucose results are summarised in Table 2, showing the blood glucose levels achieved on day 1, the rest of the stay and whole stay. Over the entire cohort, the highest median value of the glucose concentration for all three categories occurred on the first day. On the first day, the blood glucose levels achieved using Glargine only is a lot higher than the clinical data, and also higher than if intravenous insulin is incorporated. This result is also observed in Figure 1. For the rest of the stay, the Glargine only protocol is still disadvantaged compared to the other protocols. The protocol utilising a "priming" intravenous insulin injection and more Glargine on the first day achieved very similar results to the clinical data. None of the protocols resulted in hypoglycaemic events.

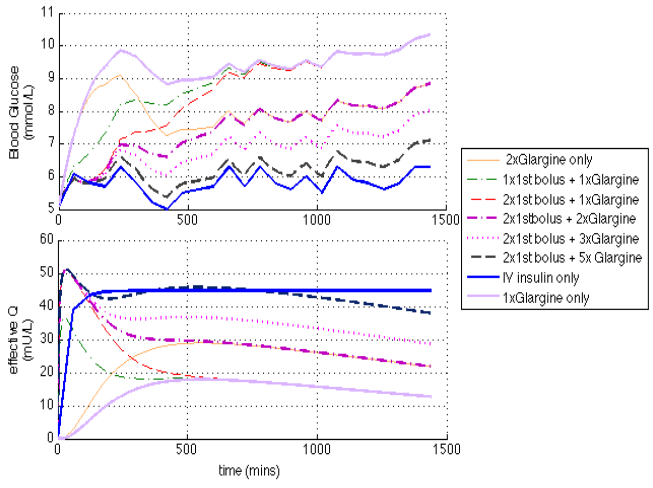

Figure 3. Effect of Glargine and priming bolus dosing on the effective interstitial insulin concentration *Q(t)*, which determines the final glucose lowering effect observed. The goal is to match the IV insulin only line for equal control.

Table 2. Cohort results (all patient hours)

	Median [IQR]	90%CI*	#Hypo<2.2
Day 1			
G^	9.7 [9.0, 10.9]	[7.6,12.7]	0
G+IV#	6.8 [6.1, 7.9]	[4.8,10.2]	0
Clinical~	6.2 [5.5, 7.3]	[4.4,9.6]	0
Rest of Stay			
G^	7.5[6.4, 8.9]	[5.1,10.6]	0
G+IV#	6.3 [5.5, 7.3]	[4.5, 9.7]	0
Clinical~	5.9[5.3,6.8]	[4.6,8.6]	0
Whole Stay			
G^	8.0 [6.7, 9.4]	[5.2,11.5]	0
G+IV#	6.5[5.6,7.5]	[4.6,9.7]	0
Clinical~	6.0 [5.3, 6.8]	[4.6,9.0]	0

* CI = confidence interval, ^ G = Glargine only, # G+IV = Glargine and intravenous insulin, ~ Clinical = Clinical SPRINT data (Chase et al, 2008)

Figures 4-6 summarise the glycaemic control obtained as cumulative distribution functions for the median, 5th and 95th percentile patients across the cohort. They clearly show the differences in the tightness and variability of the glycaemic control resulting from the different protocols. Overall, the switch to subcutaneous insulin from intravenous insulin dosing results in some loss of control despite the relatively more stable cohort used. However, relatively similar control is obtained for Glargine using the priming intravenous insulin compared to the original SPRINT clinical data, which is the primary goal in this study. Glargine alone shows a significant loss of control for the median and 90%CI patient results due to the lower effective insulin levels it achieves initially, as seen in Figure 3.

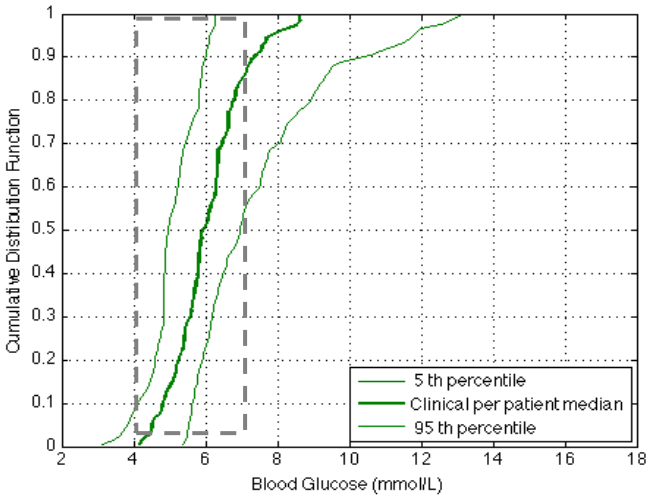

Figure 4. Clinical (SPRINT) per-patient blood glucose cumulative distribution function (CDF). Dashed box shows 4-7 mmol/L band. The median patient has 85% of measurements below 7 mmol/L in this case. The 95th percentile patient has only ~50% below this value, and the 5th percentile patient has almost 100% of blood glucose values below 7 mmol/L. Overall, the per-patient CDFs indicate the tightness across patients in the cohort.

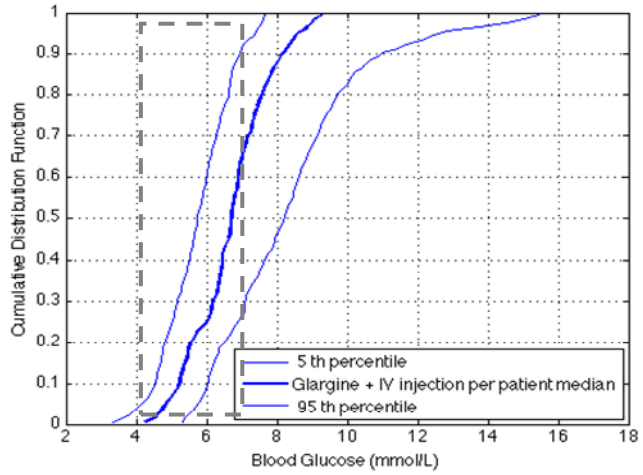

Figure 5. Glargine and intravenous IV per-patient blood glucose CDF. Dashed box shows 4-7 mmol/L band.

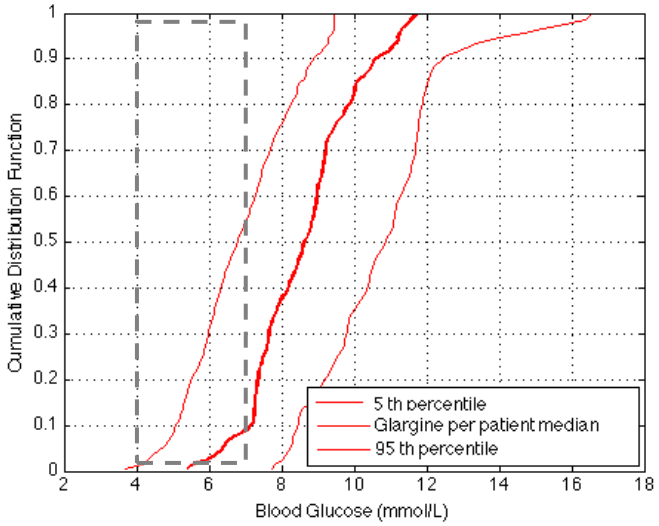

Figure 6. Glargine only per-patient glucose CDF. Dashed box shows 4-7 mmol/L band.

5. DISCUSSION

The efficacy of subcutaneously injected Glargine as basal insulin support is demonstrated in this study. Glargine is a slow, long acting insulin that goes through 4 compartments before reaching plasma. Therefore, its effect in the interstitial compartment builds up very slowly compared to intravenous insulin. It is an effective basal support for Type 1 diabetic patients on a daily basis. However, for a hyperglycaemic patient in the ICU or HDU, using Glargine alone cannot quickly reduce significantly elevated glycaemic levels, and a priming dose approach is required.

The SPRINT protocol utilises intravenous insulin injections on an hourly basis to manage glycaemic levels for critically ill patients. Many critically ill patients have volatility requirements from hour to hour. This is a result of their critical illness and the medical interventions and drug therapies they receive (Chase et al., 2008). Therefore, intravenous insulin injections suit this situation well because the response is fast and does not linger when patient metabolic status changes. Most importantly, if a patient is being weaned from inotropes or other medications that suppress insulin sensitivity, any lingering effect of insulin is undesirable because insulin sensitivity may quickly recover and result in hypoglycaemia.

For the patients studied in this paper, their insulin requirement is generally very stable and consistent from one hour to the next. These patients's insulin requirements can be substituted by Glargine successfully, as they need only a constant and stable supply of effective insulin in the interstitial compartment. However, by using Glargine only, the effective insulin in the interstitial compartment does not build up quickly to address the initially elevated blood glucose levels. Therefore it was found that using twice the insulin bolus size specified by the SPRINT protocol as a "priming" intravenous insulin bolus, together with 5 times the required intravenous insulin as Glargine, a similar profile of effective interstitial insulin can be achieved to that of SPRINT clinical data on the first day. After this priming first day, a daily subcutaneous Galrgine injection of the equivalent amount of required intravenous insulin can be used to maintain the blood glucose levels in the desirable range effectively.

According to Gerich et al (2006), it has been difficult for patients and physicians to sufficiently titrate basal insulin therapy for the fear of hypoglycaemia associated with (NPH) or Ultralente. Glargine however enables attainment of near normoglycaemia with lesser risk. This study successfully demonstrated a safe approach to use Glargine with regard to hypoglycaemia in these units. In general, the use of Glargine results in blood glucose levels slightly on the higher side compared to using intravenous insulin injections only. This result thus provides a safe and conservative alternative to glycaemic management in the ICU and HDU which is less labour intensive.

Before this work can be extended to clinical studies in the HDU, several issues still need to be addressed. HDU patients often have meals rather than a constant naso-gastric feed used in the ICU. It is known for healthy individuals, endogenous insulin is secreted upon consumptions of food (Woods et al. 1998). However it is not known to what degree HDU patients are able to support their own prandial insulin requirement. In addition, the variability in patient endogenous insulin responses will need to be addressed. Endogenous glucose production for HDU patients may be different from ICU patients as well. All these issues should ideally be investigated through clinical data gathering.

6. CONCLUSIONS

This paper presented a validated Glargine and intravenous insulin-glucose pharmacodynamic model. The in-silico virtual trial results for 16 stable ICU patients showed that Glargine can provide effective blood glucose management for these patients. An initial intravenous injection and higher Glargine dosing is required for the first day to quickly lower elevated blood glucose level. Once the patient's blood glucose levels are within a desirable range, Glargine alone can provide effective glycaemic management, reducing

nursing effort. The overall results show one approach to managing the intravenous to subcutaneous insulin transition that occurs as patients leave intensive care for less acute wards during their hospital stay. Safe, effective approaches to this transition will ensure that clinical burden and workload are not increased, while maintaining the benefits of tight glycemic control.

REFERENCES

Bistrian, BR (2001). Hyperglycemia and Infection: Which is the Chicken and Which is the Egg? *JPEN J Parenter Enteral Nutr*, 25: 180-181.

Capes SE, Hunt D, Malmberg K, Gerstein HC (2000). Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 355: 773-778.

Chase, JG, Shaw, GM, Lin, J, Doran, CV, Hann, CE, Robertson, MB, Browne, PM, Lotz, T, Wake, GC and Broughton, R (2005). "Adaptive bolus-based targeted glucose regulation of hyperglycaemia in critical care," *Medical Engineering and Physics*, 27(1), pp. 1-11.

Chase, JG, Shaw, GM, Lotz, T, LeCompte, A, Wong, XW, Lin, J, Lonergan, T, Willacy, M and Hann, CE (2007). Model-based Insulin and Nutrition Administration for Tight Glycaemic Control in Critical Care. *Current Drug Delivery*, 4(4), pp. 283-296.

Chase, JG, Andreassen S, Jensen K,. Shaw, GM (2008). Impact of Human Factors on Clinical Protocol Performance: A Proposed Assessment Framework and Case Examples. Journal of Diabetes Science and Technology.Volume 2, Issue 3, May 2008.

Chase, JG, Shaw, GM , Le Compte AJ, Lonergan ,TR, Willacy M, Wong XW, Lin J, Lotz T, Lee DS, Hann CE (2008). Implementation and evaluation of the SPRINT protocol for tight glycaemic control in critically ill patients: a clinical practice change. *Critical Care*,12:R49.

Gerich John Becker Reinhard H A; Zhu Ray; Bolli Geremia B. (2006). Fluctuations of serum basal insulin levels following single and multiple dosing of insulin glargine. *Diabetes technology & therapeutics,* 8(2):237-43.

Goldberg PA, Siegel MD, Sherwin RS, et al. (2004). Implementation of a safe and effective insulin infusion protocol in a medical intensive care unit. *Diabetes Care*, 27: 461-467.

Gubern C, Lopez-Bermejo A, Biarnes J, Vendrell J, Ricart W, Fernandez-Real JM (2006). Natural antibiotics and insulin sensitivity: the role of bactericidal/permeability-increasing protein. *Diabetes* 55: 216-224.

Hann, CE, Chase, JG, Lin, J, Lotz, T, Doran, CV, and Shaw, GM (2005). Integral-Based Parameter Identification For Long-Term Dynamic Verification Of A Glucose-Insulin System Model. *Computer Methods and Programs in Biomedicine,* 77(3), pp. 259-270.

Krinsley JS (2004). Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 79: 992-1000.

Lin, J, Lee, DS, Chase, JG, Shaw, GM, LeCompte, A, Lotz, T, Wong, XW, Lonergan, T and Hann, CE (2007). Stochastic Modelling of Insulin Sensitivity and Adaptive Glycemic Control for Critical Care. *Computer Methods and Programs in Biomedicine*. June 2007.

McCowen KC, Malhotra A, Bistrian BR (2001) Stress-induced hyperglycemia. *Crit Care Clin* 17: 107-124.

Mizock BA (2001) Alterations in fuel metabolism in critical illness: hyperglycaemia. Best Pract Res *Clin Endocrinol Metab* 15: 533-551.

Woods SC, Seeley RJ, Porte D, Schwartz, MW (1998). Signals That Regulate Food Intake and Energy Homeostasis. *Science,* 280(5368), 1378 – 1383

Van den Berghe, G, Wouters, P, Weekers, F, Verwaest, C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande, P, Lauwers P, Bouillon R (2001). Intensive insulin therapy in the critically ill patients. *N Engl J Med* 345: 1359-1367.

Van den Berghe, G, Wilmer, A, Hermans, G, Meersseman, W, Wouters, PJ, Milants, I, Van Wijngaerden, E, Bobbaers H, Bouillon, R (2006). Intensive Insulin Therapy in the Medical ICU. *N Engl J Med* 354: 449-461.

Whitehorn, LJ (2006). A review of the use of insulin protocols to maintain normoglycaemia in high dependency patients. *Journal of Clin Nursing* 16: 16-27.

Wong, Jason. Geoffrey Chase, Christopher E. Hann, Geoffrey M. Shaw, Thomas F. Lotz, Jessica Lin, and Aaron LeCompte (2008a). *In Silico* Simulation of Long-Term Type 1 Diabetes Glycemic Control Treatment Outcomes. *Journal of Diabetes Science and Technology*.Volume 2, Issue 3, May 2008

Wong, Jason. Geoffrey Chase, Christopher E. Hann, Geoffrey M. Shaw, Thomas F. Lotz, Jessica Lin, and Aaron LeCompte (2008b). Development of a Clinical Type 1 Diabetes Metabolic System Model and *in Silico* Simulation Tool. *Journal of Diabetes Science and Technology*.Volume 2, Issue 3, May 2008

Wong, Jason. Geoffrey Chase, Christopher E. Hann, Geoffrey M. Shaw, Thomas F. Lotz, Jessica Lin, and Aaron LeCompte (2008c). Simulation in a Diabetes Decision Support Role: Model Structure and Parameter Identification. *Journal of Diabetes Science and Technology*. Volume 2, Issue 4, July 2008

Wong, Jason. Geoffrey Chase, Christopher E. Hann, Geoffrey M. Shaw, Thomas F. Lotz, Jessica Lin, and Aaron LeCompte (2008d). A Subcutaneous Insulin Pharmacokinetic Model for Computer Simulation in a Diabetes Decision Support Role: Validation and Simulation. *Journal of Diabetes Science and Technology*.Volume 2, Issue 4, July 2008.