Meal Disturbance Effect on Control of Blood Glucose Level for Critically-ill Patients using In-silico Works

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Abstract. This study was conducted to determine the effect of meal disturbance on blood glucose level of the critically ill patients and to simulate the control algorithm previously developed using in-silico works. The study is significant so as to reduce the mortality rate of critically ill patients who usually encounter hyperglycaemia or/and hypoglycaemia while in treatment. The meal intake is believed to affect the blood glucose regulation and causes the hyperglycaemia to occur. Critically ill patients receive their meal through parenteral and enteral nutrition. Furthermore, by using in-silico works, time consumed and resources needed for clinical evaluation of the patients can be reduced. Hovorka model was employed in which the simulation study was carried out using MATLAB on the virtual patient and it was being compared with actual patient in which the data were provided by Institut Jantung Negara (IJN). Based on the simulation, the disturbance on enteral glucose supplied had affected the blood glucose level of the patient; however, it remained unchanged for the parental glucose. To reduce the occurrence of hypoglycaemia and hyperglycaemia, the patient was injected with 30 g/hr and 10 g/hr of enteral glucose, respectively. In conclusion, the disturbance of meal received can be controlled through in-silico works.

1. Introduction

A critically-ill patient is defined as the patient who has high risk for actual or potential fatal health problems. They are usually highly unstable, weak and complicated; hence intense and attentive nursing cares are mostly needed by those patients. The critically-ill patient is normally diagnosed with hyperglycaemia, although the patient has no diabetes history in the past [1]. Hyperglycaemia is a phenomenon in which the body contains high blood glucose (more than 6.6 mmol/L) due to the lack of insulin in the body or the insulin present is not effectively used by the body. Its occurrence in critically-ill patients is due to the release of counter-regulatory stress hormones which are known as corticosteroids and cathecholamines [2]. Another phenomenon which is the contradictory to hyperglycaemia is known as hypoglycaemia in which patient's body contains a low blood glucose level (below 4.0 mmol/L). Hypoglycaemia also contributes to the mortality and morbidity rates of critically-ill patients when they go through an intensive glucose control [3].Unlike other patients, critically-ill patients eat their meal through enteral or parenteral nutrition or both [4-10]. Enteral nutrition is one of the ways to deliver food to the stomach or small intestine using tubes whereas parenteral nutrition is a method of delivering the nutrition into the body through veins, which is also known as intravenous feeding. In this research, the intake of the nutrition is crucial as it influences the blood glucose level of the patients and thus, affecting the glucose insulin control of the patients.

The meal intake of the critically-ill patients disturbs the blood glucose level in the body. Whenever the patients receive nutrition by either enteral or parenteral nutrition, the blood glucose level in their body will increase and it consequently results in hyperglycaemia [11]. This problem might lead to a situation where it is difficult to regulate the blood glucose level of the patients in the range of 4.0 to 6.6 mmol/L. Hence, there is a need to study the effect of meal disturbance on the blood glucose control of the patients.Furthermore, most studies on intensive insulin therapy and glucose control protocols of critically-ill patients have been conducted clinically. However, the main concern to these studies is central to enormous times and resources required for the clinical assessment. Those clinical experiments might not be convenient to subjects of trial as they would affect patients physically and mentally. The need of time and resources during clinical evaluation indirectly represents financial burden to the researchers [12-14]. By using in-silico works or simulation method, the cost spent on the clinical evaluation can be reduced and the inconvenience that the patients experienced during the clinical assessment can be eliminated. In this study, mathematical equations which represent the blood glucose level of the patients are adopted from Hovorka et al. [15]. The study is conducted to determine the effect of meal disturbance on blood glucose level of the critically ill patients and to simulate the control algorithm developed through in-silico works using MATLAB.

2. Methodology

2.1 Data collection and extraction

Data collection and information of the actual patients required for the study were obtained from the Intensive Care Unit, Institut Jantung Negara (IJN), Kuala Lumpur. The data provided include patients' biodata namely; name, date of birth, gender, race, type of meal intake, glucose level, etc. Approval data from IJN ethic committee was received prior to carrying out this study. The extracted data were then filtered out to sort for the needed information related to the study. By using data filter mechanism available in MATLAB, the data were sized down to smaller numbers so as to comply with the scope of the research. The study focuses on critically-ill patients with the age ranges from 52 ±10 years and the weight of 75 ± 23 kg. The patients received meal through parenteral and enteral nutrition. The patient data were termed as clinical data throughout this study. Parameters and variables are taken from patient 5 of Hovorka model [15], fitted into equations, used as simulated data and then the simulation data were compared with IJN clinical data. Table 1 shows parameter values of critically-ill patient obtained from Hovorka[15] which were used in the simulation study using MATLAB.

Table 1. Parameter values of critically-ill patient (Patient 5)

Quantity	Symbol	Value
Renal glucose threshold	G_R(mmol/L)	10.3
Fraction to which endogenous insulin secretion is suppressed by the delivery of exogenous insulin	$F_{IE,basal}$ (unitless)	0.20
Fractional renal glucose clearance	k_r (min^{-1})	0.009
Plasma insulin concentration at which the fractional clearance of insulin is halved	$K_{M,I}$ (mU L^{-1})	564
Glucose distribution volume	V_G(L kg^{-1})	0.16
Insulin distribution volume	V_I(L kg^{-1})	0.12
Blood glucose concentration at which the non-insulin dependent glucose flux attains half of its maximum value	$K_{M,N}$ (mmol/L)	1
Fractional elimination rate extrapolated to zero insulin concentration	k_e (min^{-1})	0.15
EGP extrapolated to zero insulin concentration	EGP_0 (mmol kg^{-1} min^{-1})	0.0226
Enteral glucose bioavailability (unitless)	F_{GE} (unitless)	0.29
Plasma insulin concentration at which the fractional transfer rate k_{21} achieves half of its maximum value	$K_{M,T}$ (mU L^{-1})	15.8
Beta-cell responsiveness	M_I (mU kg$_{-1}$ min$_{-1}$ per mmol L^{-1})	0.323

Half-time suppression of endogenous insulin secretion	$t_{1/2,IE}$ (min)	88
Time-to-maximum of enteral glucose absorption	$t_{max,G}$ (min)	14
Pre-study insulin secretion	$U_{IE,basal}$ (mU kg^{-1} min^{-1})	0.39
Non-insulin-dependent glucose flux	F_{01}(mmol kg^{-1} min^{-1})	0.0104
Fractional transfer rate between the non-accessible and accessible glucose compartments	k_{12} (min^{-1})	0.063
Deactivation rate of remote insulin effect on glucose distribution/transport	k_{a1}(min^{-1})	0.0032
Deactivation rate of remote insulin effect on glucose disposal	k_{a2}(min^{-1})	0.0558
Deactivation rate of remote insulin effect on endogenous glucose production	k_{a3}(min^{-1})	0.0363
Insulin sensitivity of disposal	S_{ID} (min^{-1} per mU L^{-1})	0.0003
Insulin sensitivity of EGP	S_{IE} (per mU L^{-1})	0.072
Insulin sensitivity of distribution/transport	S_{IT} (min^{-1})	0.109

2.2 Glucose-Insulin Regulatory System Model Selection

Model of the glucose-insulin system or the algorithm to control the blood glucose level of critically-ill patients was selected from Hovorka et al. [15] which consisted of five sub-models as shown in Figure 1.

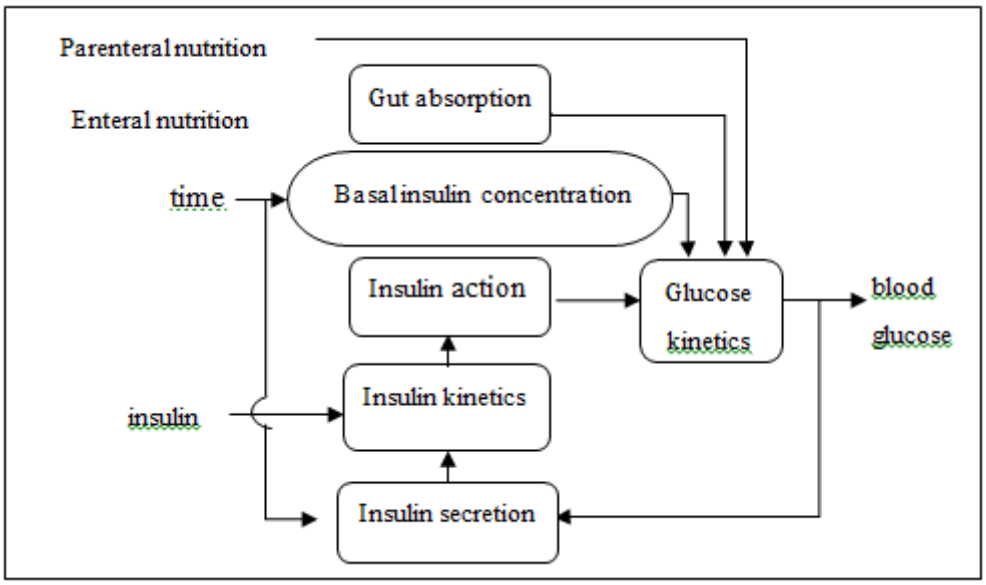

Figure 1. The glucoregulation model that combining five sub-models

a) Endogenous insulin secretion sub-model

Equations 1 and 2 represent the endogeneous insulin secretion sub-model as follows:

$$U_{\mathrm{IE}}^{u}(t) = \frac{60}{1000} W \left(M_I(G(t) - 5.5) + U_{\mathrm{IE,basal}} \left(F_{\mathrm{IE,basal}} + \left(1 - F_{\mathrm{IE,basal}}\right) \mathrm{e}^{-t \frac{\ln(2)}{t_{1/2,\mathrm{IE}}}} \right) \right) \quad (1)$$

$$U_{\mathrm{IE}}(t) = \begin{cases} U_{\mathrm{IE}}^{u}(t), & \texttt{if } U_{\mathrm{IE}}^{u}(t) > 0 \\ 0, \end{cases} \quad (2)$$

Otherwise

Where $U_{\mathrm{IE}}^{u}(t)$ and $U_{\mathrm{IE}}(t)$ are the unconstrained and actual endogenous insulin secretions at time t, respectively with unit of U h^{-1}, W is the subject's weight (kg), M_I is the beta-cell responsiveness expressing the ability of the beta cell to step up insulin secretion when glucose deviates from the entering glucose concentration of 5.5 mmol/L (mU kg^{-1} min^{-1} per mmol L^{-1}), $U_{\mathrm{IE,basal}}$ represents the basal insulin secretion (mU kg^{-1} min^{-1}), $F_{\mathrm{IE,basal}}$ is the fraction where endogenous insulin secretion is suppressed by the delivery of exogenous insulin (unitless) and $t_{1/2,\mathrm{IE}}$ is the half-time of the suppression of endogenous insulin secretion by exogenous insulin (min).

b) Insulin kinetics sub-model
Equation 3 represents the insulin kinetics sub-model as follows:

$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = \frac{1000}{60W}\frac{U_{\mathrm{IX}}(t) + U_{\mathrm{IE}}(t)}{V_I} - k_e \frac{K_{M,I}}{I(t) + K_{M,I}} I(t) \tag{3}$$

Where $I(t)$ is the plasma insulin concentration (mU L^{-1}), $U_{\mathrm{IX}}(t)$ is the infusion of the exogenous insulin (Uh^{-1}), k_e is the fractional elimination rate extrapolated to zero insulin concentration (min^{-1}), $K_{M,I}$ is the plasma insulin concentration at which the fractional clearance of insulin is divided by two (mUL^{-1}) and V_I is the insulin distribution volume (Lkg^{-1}).

c) Enteral glucose absorption sub-model
Equations 4 and 5 represent the enteral glucose absorption sub-model as follows:

$$\frac{\mathrm{d}A_1(t)}{\mathrm{d}t} = \frac{F_{\mathrm{GE}}U_{\mathrm{GE}}(t)}{60} - \frac{\mathrm{A}_1(t)}{t_{\mathrm{max},G}} \tag{4}$$

$$\frac{\mathrm{d}A_2(t)}{\mathrm{d}t} = \frac{A_1(t)}{t_{\mathrm{max},G}} - \frac{\mathrm{A}_2(t)}{t_{\mathrm{max},G}} \tag{5}$$

Where A_1 and A_2 are two compartments that form a chain representing absorption of enteral glucose (g), F_{GE} is the bioavailability of enteral glucose (unitless), $U_{\mathrm{GE}}(t)$ is the administration of enteral glucose (g h^{-1}) and $t_{\mathrm{max},G}$ is the time-to-maximum of enteral glucose absorption (min).

d) Insulin action sub-model
Equations 6 to 8 represent the insulin action sub-model as follows:

$$\frac{\mathrm{d}x_1}{\mathrm{d}t} = -k_{\mathrm{a1}}[x_1(t) - I(t)] \tag{6}$$

$$\frac{\mathrm{d}x_2}{\mathrm{d}t} = -k_{\mathrm{a2}}[x_2(t) - I(t)] \tag{7}$$

$$\frac{\mathrm{d}x_3}{\mathrm{d}t} = -k_{a3}[x_3(t) - I(t)] \tag{8}$$

And x_1, x_2 and x_3 are the (remote) effects of insulin on glucose transport, glucose disposal and endogenous glucose production (mU L^{-1}) while k_{ai}, i = 1,…, 3, represent deactivation rate constants (min^{-1}).

e) Glucose kinetics sub-model
Equations 9 to 11 represent the glucose kinetics sub-model as follows:

$$\frac{dQ_1(t)}{dt} = -F_{01}^c - k_{21}(t)Q_1(t) + k_{12}Q_2(t) - U_R(t) + \frac{5.551}{W}\left[\frac{U_{GP}(t)}{60} + \frac{A_2(t)}{t_{max,G}}\right] + EGP(t) \quad (9)$$

$$\frac{dQ_2(t)}{dt} = k_{21}(t)Q_1(t) - \left[k_{12} + S_{I,MOD}(t)S_{ID}x_2(t)\right]Q_2(t) \quad (10)$$

$$G(t) = \frac{Q_1(t)}{V_G} \quad (11)$$

$Q_1$and Q_2(mmol/kg) indicate the masses of glucose in the accessible compartment and non-accessible compartment respectively, k_{12}(min^{-1}) is the transfer rate constant from the non-accessible to the accessible compartment, V_G (L kg^{-1}) is the distribution volume of the accessible compartment, $U_{GP}(t)$ is the parenteral glucose infusion (g h^{-1}), G (mmol/L) is the blood glucose concentration, S_{ID} is the insulin sensitivity of glucose disposal (min^{-1} per mU L^{-1}), $S_{I,MOD}$ is the insulin sensitivity modifier, and EGP_0 is the endogenous glucose production (EGP) extrapolated to the zero insulin concentration. F_{01}^c is the total non-insulin dependent glucose flux corrected for the ambient glucose concentration while $U_R(t)$ (mmol kg^{-1} min^{-1}) is the renal glucose clearance above the glucose threshold of G_R (mmol/L).

3. Results and discussion

3.1 Blood glucose level (BGL) of patients from clinical study and simulation

Figure 2 shows the comparison between the blood glucose level (BGL) of a critically ill patient from Hovorka work in 2008 (Patient 5) [15] with the actual patient from the clinical study (Patient X) in which the data was provided by Institut Jantung Negara.

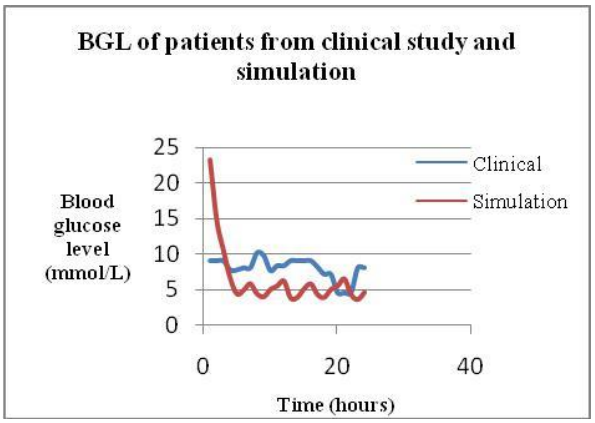

Figure 2. Blood glucose level of patients from clinical study and simulation

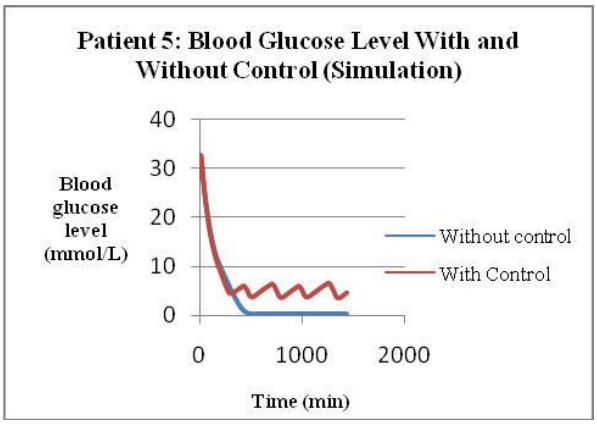

Figure 3. Blood glucose level of Patient 5 with and without control (simulation)

It can be seen that the BGL pattern for both patients are quite similar. Although at the beginning hours the BGL of patient from simulation work was quite high i.e. 23.3 mmol/L

and only 9.1 mmol/L for patient from the clinical study, the difference in blood glucose concentration as well as the BGL patterns for both patients was not too large beginning at about the fifth hour. Hence, both patients i.e. Patient X and Patient 5 have been chosen to be discussed in this study. Hovorka et al. [15] did not specifically disclose the information of all six patients in his paper. However it was known that those patients consist of three males and three females, age 52 ±10 years and weight of 75 ± 23 kg.

3.2 The difference of blood glucose level for Patient 5 with and without control

Figure 3 illustrates the simulation of two types of blood glucose level of a critically ill patient in two situations; without control and with control. Both conditions with control and without control showed the same pattern at the beginning of the simulation. The blood glucose level increased slightly from 28.1 mmol/L at 0 minute to 32.7 mmol/L at 10.8 minutes. For the simulation which included control, it decreased significantly to 4.5 mmol/L at 300 minutes. After that the blood glucose level was regulated in the safe range which was between 4.4 and 6.6 mmol/L. The lowest level was about 3.5 mmol/L at time 1358 minutes while the highest level was 6.6 mmol/L from 1254 to 1268 minutes. Without any control, the blood glucose level kept decreasing to 0.2 mmol/L at 519 minutes and remained constant until 1440 minutes. This condition resulted in hypoglycaemia at which the blood glucose concentration of a person fell below 4.0 mmol/L and could cause death [3]. The control scheme mentioned above can be explained by controlling the amount of parenteral and enteral glucose which was received by the patients as their meal or nutrition. A more detailed discussion on enteral and parenteral glucose disturbance is provided in the next section.

3.3. Blood glucose level of patient 5 for different amount of enteral glucose

Figure 4 shows three different patterns of blood glucose level for three different amounts of enteral glucose (Uge); namely 30, 60 and 130 g/hr. All of them showed the same pattern at the beginning where at 0 minute the BGL was 28.1 mmol/L and it increased slightly to 32.7 mmol/L at time 10.8 until 14.5 minutes.

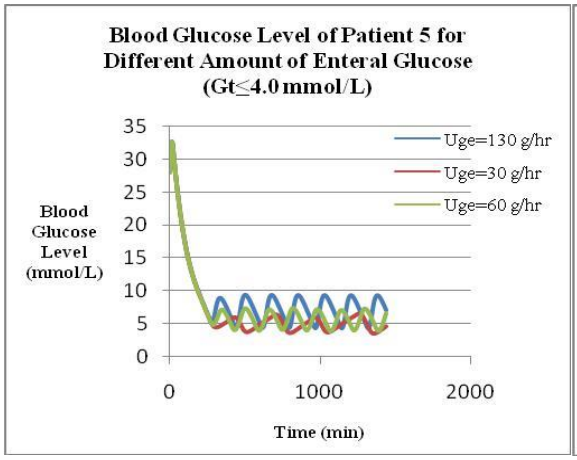

Figure 4. Blood glucose level of Patient 5 for different amount of enteral glucose (Gt≤4.0 mmol/L)

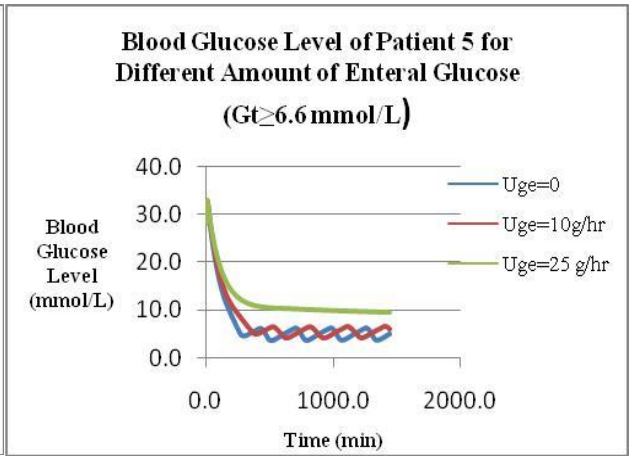

Figure 5. Blood glucose level of Patient 5 for different amount of enteral glucose (Gt≥6.6 mmol/L)

After that, the BGL decreased significantly to 5 mmol/L and began to fluctuate. It can be seen that for the highest amount of Uge, which was 130 g/hr, the BGL was higher than the other two. The BGL fluctuated within 4.3 to 9.3 mmol/L. The hyperglycaemia case could be observed in this situation. When Uge supplied was 60 g/hr, the BGL fluctuated within 3.9 to

7.5 mmol/L. Meanwhile for Uge equals to 30 g/hr, the BGL fluctuates within 3.3 to 6.6 mmol/L. Although there was occurrence of BGL fell below 4.0 mmol/L, it only occurred for a few minutes .This clearly indicated that 30 g/hr of enteral glucose was preferred to be the amount of enteral glucose that should be injected to Patient 5 to control his/her blood glucose in a safe range. Figure 5 depicts how different amount of enteral glucose affects the blood glucose control when the BGL is more than or equal to 6.6 mmol/L.

When patient was not injected with any Uge, like previously the BGL increased sharply from 28.1 to 32.7 mmol/L before it slowly decreased to 4.5 mmol/L. The BGL then fluctuated with the lowest value of BGL recorded was 3.6 mmol/L and the highest value of BGL recorded was 6.2 mmol/L. As the patient was injected with 10 g/hr of enteral glucose, the BGL pattern seemed better as the lowest value of BGL recorded was 4.1 mmol/L and the highest value of BGL recorded was 6.5 mmol/L. Meanwhile, with 25 g/hr of Uge, the patient's BGL seemed to regulate within 10 mmol/L and showed little change from time to time. It indicated that a case of hyperglycaemia might occur if 25 g/hr of Uge was supplied to the patient when his/her BGL was more than or equal to 6.6 mmol/L. Hence, for patient 5 to regulate his/her BGL within the safe range, 10 g/hr of enteral glucose was the best option

3.4. Blood Glucose Level of Patient 5 for Different Amount of Parenteral Glucose

Figures 6 and 7 show that for three different amount of parenteral glucoses (Ugp), the pattern of BGL is the same. There was no difference shown in the regulation of BGL. In Figure 6, the BGL increased shortly from 28.1 mmol/L to 32.1 mmol/L before it slowly decreased to 4.0 mmol/L at 427 minutes. The BGL increased and then decreased with the lowest value of BGL recorded 3.8 mmol/L and the highest value of BGL recorded was 6.4 mmol/L. Just like the previous figure, the BGL of Patient 5 in Figure 7 was initially 28.1 mmol/L.

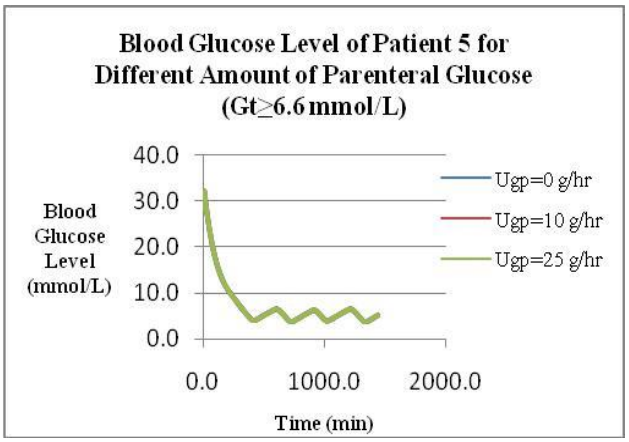

Figure 6. Blood glucose level of Patient 5 for different amount of parenteral glucose (Gt>6.6mmol/L)

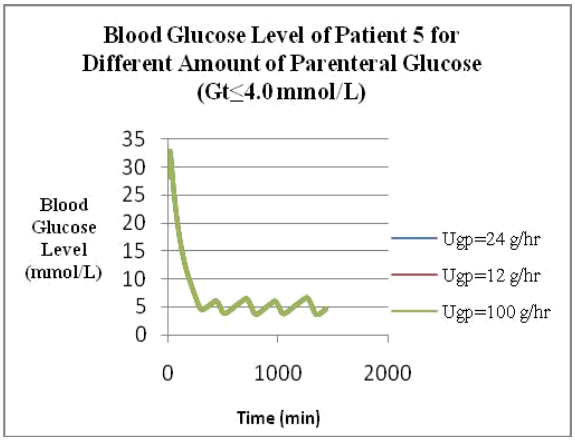

Figure 7. Blood glucose level of Patient 5 for different amount of parenteral glucose(Gt≤4mmol/L)

The BGL increased slightly to 32.7 mmol/L before it decreased dramatically to 4.5 mmol/L at 300 minutes. Starting at this point, the BGL fluctuated within the range of 3.6 to 6.6 mmol/L. Both figures showed that there was a little chance for hypoglycaemia to occur as the BGL fell below 4.0 mmol/L but none of hyperglycaemia case could be observed. However, both figures also tell us that with different amount of parenteral glucose supplied to patient 5, similar pattern of BGL could be observed. This indicates that by disturbing the parenteral glucose supplied to the patient, the BGL patterns are not affected. This occurrence opposes the normal situation where both enteral and parenteral nutritions contribute to the change in blood glucose level of the patient. It is suggested that modification on equations

which involve the Uge should be carried out in the future study because these equations are very important to ensure that a well simulation work can be conducted so that the relationship between parenteral nutrition and blood glucose level of the patient can be examined.

The control strategy in MATLAB simulation might be lacking in terms of little correlation between meal disturbance and insulin infusion rate. The insulin infusion is one of the most active parameters in glucose-insulin control in Hovorka model [16, 17]. Insulin is needed to help the patient to regulate his blood glucose. However in this simulation, although insulin infusion had been considered as one of the input variables aside from enteral and parenteral glucoses, the value cannot be varied for different times. In previous work from Hovorka and others, the glucose-insulin control was generated where the reaction between insulin infusion rate and blood glucose level can be interpreted [15, 18, 19, 20, 21]. Therefore, it is recommended that in the future study, the equations involving insulin infusion in the simulation work could be improved to generate a more reliable result of blood glucose level of the critically-ill patient.

4. Conclusion

The objectives of the study on the effect of meal disturbance on blood glucose level as well as simulation work on control algorithm to control the blood glucose level using in-silico works for critically-ill patients were achieved. Based on the simulation, the disturbance on enteral glucose supplied affected the blood glucose level of the patient. To reduce the occurrence of hypoglycaemia and hyperglycaemia, the patient was injected with 30 g/hr and 10 g/hr of enteral glucose, respectively. However, the disturbance on parenteral glucose did not affect the blood glucose level of the patient. Therefore, a study should be conducted to modify the equations which involve parenteral glucose as a variable input of the model to improve the result of the simulation. Besides, it is also recommended that in the future study, the equations concerning insulin infusion rate in the simulation work could be improved to generate a more reliable result of blood glucose level of the patient.

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