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WORD COUNT	2489	TIME SUBMITTED	26-NOV-2024 03:49PM
		PAPER ID	113170000

Type of article: Clinical study

Implementing Glycaemic Control Protocol in the surgical intensive care unit

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ABSTRACT

Background. Hyperglycaemia and insulin resistance are common in critically ill patients, resulting in increased morbidity and mortality. Although tight glycaemic control can reduce complications, the optimal target blood glucose level remains unclear. This study evaluated an individualized, nurse-driven glycaemic protocol in a surgical intensive care unit with the primary outcome of more time spent in cumulative time in the band.

Methods. This study was conducted in the Surgical Intensive Care Unit and involved surgical

patients over 18 years of age with diabetes, an APACHE 2 score greater than 15, and those requiring postoperative intensive care. The protocol group followed a nurse-driven glycaemic control protocol using a dynamic algorithm for insulin administration. In the control group, insulin was administered at the discretion of the physician. Blood glucose levels were monitored every 2 h, aiming at 8-11 mmol/L. Data from 53 protocol group patients and 37 control group patients were analyzed.

Results. The protocol significantly reduced episodes of moderate-to-severe hypoglycaemia compared to the control group. The primary outcome, cumulative time in the target glycaemic range, was greatly improved in the protocol group. Additionally, the modified glycaemic penalty index indicated better performance of the protocol compared to that of the control.

Conclusions. An individualised nurse-driven glycaemic protocol is a safe and effective method for managing hyperglycaemia in critically ill surgical patients, improving the time in the target glycaemic range without increasing the risk of hypoglycaemia. These findings support further research on closed-loop algorithms and lower-target values.

Keywords: Hyperglycaemia; Hypoglycaemia; Insulin Therapy; Glycaemic Control; Intensive Care Unit; Diabetes Management

KEY MESSAGES

•Individualised nurse-driven glycaemic control protocol in the surgical intensive care unit (ICU) significantly reduces episodes of moderate-to-severe hypoglycaemia and improves the

cumulative time within the target glycaemic range.

•Personalised and dynamic insulin administration, facilitated by a specially designed algorithm, enhances patient safety and glycaemic control compared to traditional physician-determined methods.

•These findings suggest that further research into closed-loop systems and lower glucose targets is warranted to potentially improve outcomes in critically ill surgical patients.

INTRODUCTION

Hyperglycaemia and insulin resistance are common in critically ill patients because of their response to acute stress and systemic inflammation. The degree of insulin resistance is proportional to the disease severity. Hyperglycaemia during critical illness is associated with increased morbidity and mortality rates [1,2]. This risk is even higher in patients without a history of diabetes. However, complications associated with artificial nutrition are more common in diabetic patients [3].

Diabetes is a highly prevalent metabolic disorder, affecting as many as 20-40% of hospitalized general surgery patients [4]. Type I diabetes is caused by decreased insulin production due to destruction of pancreatic beta cells. It is essential to provide exogenous insulin to DM type I patients, and requirements increase during critical illness due to insulin resistance [5]. In Western countries, type II diabetes is more prevalent owing to lifestyle and an increasing prevalence of obesity [6,7]. Initially, insulin resistance is the main feature, but later due to exhaustion of insulin production, there is a need for exogenous insulin administration. During critical illness, there is a combination of insulin resistance and decreased insulin secretion, and many patients require insulin therapy, especially in the setting of artificial nutrition [8,9].

Considering the possible complications of hyperglycaemia, intensive insulin therapy with a target blood glucose of 4.4 – 6.1 mmol/l (tight glycaemic control) may decrease morbidity and mortality in the Intensive Care Unit (ICU). In 2001, Van den Berghe et al. published results on intensive insulin therapy in critically ill patients and demonstrated a remarkable decrease in overall in-hospital mortality by 32%, bloodstream infections by 46%, and acute renal failure requiring renal replacement therapy by 41% [10]. After the Leuven trial, several implementation studies and single-center Randomized control trials (RCTs) have confirmed that tight glucose control is associated with improved outcomes, including mortality. However, in 2009, the largest RCT, NICE-SUGAR, found that this approach caused excessive mortality, which was attributed to episodes of severe hypoglycaemia [11].

The optimal blood glucose level in patients with critical illnesses is not yet known. Current guidelines suggest moderate glycaemic control, in which insulin therapy is started once blood glucose exceeds 10 mmol/l and then administered by continuous infusion to maintain levels between 8-10 mmol/l [12,13]. The approach to glucose control may differ between diabetic and non-diabetic patients [14]. In diabetic patients, hypoglycaemia and glucose variability have a greater influence on the outcome, while hyperglycaemia may be of greater importance in non-diabetic patients [15]. Liberal glucose control with glucose levels between 10 and 14 mmol/l seems to be safe for diabetic patients [16]. In addition, the optimal insulin delivery method is still under discussion. The factors that need to be considered include episodes of hypoglycaemia, blood glucose levels prior to admission as well as glucose variability. Preiser et al. discussed the importance of standardizing measures for glucose monitoring devices and automated systems to ensure the accuracy and quality of glucose control in the ICU and general wards [17].

At our institution, no insulin administration protocol has been used before 2019. Insulin therapy

was administered at the discretion of the prescribing physician, either by bolus or continuous infusion, with no strict target values. This resulted in high glucose variability and frequent episodes of hypoglycaemia. In addition, many deranged blood glucose levels were undetected owing to non-uniform measurement intervals. Therefore, we aimed to design a monitoring and insulin administration system.

METHODS

We conducted a study evaluating a novel dynamic glycaemic protocol in the Surgical Intensive Care Unit after obtaining approval from the ethics board. The study started in January 2019 but was interrupted due to the COVID-19 pandemic and was restarted in October 2022. It involved surgical patients older than 18 years who were diabetic, had an APACHE 2 scoring system greater than 15, and required postoperative intensive treatment. Patients with diabetic ketoacidosis, hyperosmolar coma, severe distributive shock, or microvascularisation disorders were excluded. In addition, protocols that lasted less than 24 hours were excluded. The main outcome was better glycaemic control, measured by more time spent in cumulative time in band (cTIB), and the secondary outcome was the prevention of hypoglycaemic episodes.

In the Protocol group, nurses took care of the patient according to an individualized, goal-directed, nurse-driven glycaemic protocol (protocol group), while in the control group, the amount of insulin was determined by the doctor on duty. The control group was obtained by searching the departments' medical archives using the same inclusion and exclusion criteria. The blood glucose level (BGL) in the protocol group was managed according to a dynamic algorithm that considered the previous BGL as well as the change in the current BGL in relation to the previous BGL to determine the speed of insulin flow.

The protocol was initiated at a BGL of 11 mmol/L for two consecutive measurements. Once the protocol was initiated, glycaemic control was performed every 2 h from the drop of blood

from the finger. The device was a hospital standard calibrated daily (Accu-Check Inform II, Roche Diagnostics, Germany), and the target values were 8–11 mmol/L since liberal glucose control is safe in the group of diabetic critically ill patients with respect to mortality rates and results in fewer hypoglycaemic episodes [15]. For values below 8 mmol/L, insulin infusion was stopped, and glycaemic control was carried out every hour. If the BGL was below 4 mmol/L, checks were performed every 30 min.

Patients who stayed in the ICU for less than 24 h and those who had deviations from the protocol were excluded. The total number of patients in the protocol was 60, of which 7 were excluded due to incomplete data. Data processing was initiated for 53 patients. A control group of 37 patients was included in the retrograde analysis from the archive, using the same inclusion criteria (Figure 1).

For easier and faster application of the protocol, an Android application (APP) in the programming language JAVA was developed for devices with an Android operating system. The application was installed on a tablet that was available to medical technicians and nurses in the ICU. The application enabled the automatic calculation of insulin flow rate values and insulin bolus values and suggested procedures according to the protocol.

The primary outcome of the study was cumulative time in band (cTIB), a useful parameter to describe glucose control performance that calculates the proportion of time that blood glucose values are within the desired range and indicates both blood glucose levels and glucose variability. The secondary outcomes were episodes of hypoglycaemia, time spent in moderate and severe hypoglycaemia, variability of glycaemia, and evaluation of the protocol itself.

The protocol itself was evaluated using the glycaemic penalty index (GPI), which was proposed for the first time in 2008 as a tool for assessing overall glycaemic control behavior in ICU patients by Van Herpe [18]. The original GPI of a protocol is the average of all penalties that

are individually assigned to each measured BGL value based on the optimized smooth penalty function. The computation of this index returns a number between 0 (no penalty) for measurements targeting a BGL of 80 to 110 mg/dl and 100 (the highest penalty) for extremes. Two parameters were found to have a significant impact on the GPI: the BGL sampling frequency and duration of the algorithm application. A higher BGL sampling frequency and a longer algorithm application duration resulted in an apparently better performance, as indicated by a lower GPI [18].

The mathematical computation of Van Herpe's GPI was adjusted by the authors for the ICU BGL target and measuring units (mmol/L). According to the formula $y= 32,1288*(8-BGL)^{0,6337}$ for hypoglycaemic measurements (below 8 mmol/L), and $y= 40,3834*(BGL-11)^{0.5635}$ for hyperglycaemic measurements (above 11 mmol/L), not penalizing BGL between 8 and 11 mmol/L, the values were in the range and a maximum of 100 for extremes in both directions of hyperglycaemia and hypoglycaemia (figure 2). Thus, the modified GPI (mGPI) was used to compare and evaluate protocols.

The data were processed using SPSS 27 (IBM, USA). The Pearson χ^2 test was used for categorical variables and independent Student's t-test for parametric variables and, with CI 95%, Alpha 0,05 and observed power 0,99.

RESULTS

The results of our study showed a good safety profile of the protocol, with significantly shorter times of lowered blood glucose and higher minimum values compared to controls (Table 1). There was also a significant difference in the number of patients who had at least one episode of moderate-to-severe hypoglycaemia, favouring our protocol (7.5% vs. 51.4%; $\chi 2$ (1, N = 90) = 21.97; *p<0.001)*. Although we failed to show a difference in blood glucose variability, we significantly improved the time spent in the target levels which was our primary objective,

without a significant difference in the time spent above the upper target value. Our Cumulative time in the band was 50.8±15% vs. 33.3±16.8%; $t(88)=5.18$; $p=0.01$, in favour of Protocol *CI*(10.2; 25.6) (Figure 3). The variability in the BGL in our protocol was generally lower, but the difference was not significant. When we compared protocols with the mGPI index, our individualized, goal-directed, nurse-driven glycaemic protocol performed significantly better than Control protocol (22.2±9.9 vs 33.3±16.8; $t(88) = -5.00$; $p=0.01$, *CI*(-16.2; -7.4); Figure 4). When we compared our protocol with the predefined cutoff score of 25, we found a significantly lower penalization $t(52)=-2.10$; $p=0.041$, *CI*(-5.58; -0.12). The time spent in severe hypoglycaemia was significantly lower (Figure 5).

All analyses were performed with 1000 bootstrap samples and bias-corrected and accelerated confidence intervals.

DISCUSSION

The findings of this study show that a novel, individualised, goal-directed, nurse-driven, and APP-facilitated glycaemic protocol is a safe and effective alternative to current practices and fixed insulin dosage regimens for hyperglycaemia. We showed that this type of insulin dosing has fewer hypoglycaemic episodes and generally better control of glycaemia, spending more time in the desired range. Preiser et al. showed that hypoglycaemic episodes are directly proportional to survival [17]. Although we did not observe a difference in the variation in glucose levels, an important objective was achieved by increasing the amount of time spent within the target range. The strength of this study is its simplicity and user-friendly protocol which improved the precision of glucose management.

A limitation of our study is the lack of a real-time control group and the use of historical controls, as well as the absence of a prospective randomized study design. Using the APACHE II score, we tried to show the balance of disease severity in the study participants in both groups. These

findings open the possibility of further prospective research in the direction of closed-loop algorithms, as well as in the direction of reducing target values closer to normal values without fear of episodes of hypoglycaemia. Future research should also attempt to evaluate continuous glucose monitoring in the ICU setting.

CONCLUSION

In summary, our research indicates that a personalized, target-oriented, nurse-led glycaemic regimen assisted by a mobile application is a secure and efficient alternative to conventional insulin administration techniques for managing high blood sugar levels in critically ill patients in ICU settings. This method considerably diminished the incidence of low blood sugar episodes and extended the duration of the patient's blood glucose levels to remain within the desired range. However, it did not have a considerable impact on glucose fluctuations. Future investigations should focus on prospective studies and the potential advantages of continuous glucose monitoring in the ICU.

Figure legend:

Figure 1. Flowchart of study

Figure 2. Modified Glycemic Penalty Index

Figure 3. Difference in Cumulative time in band by groups

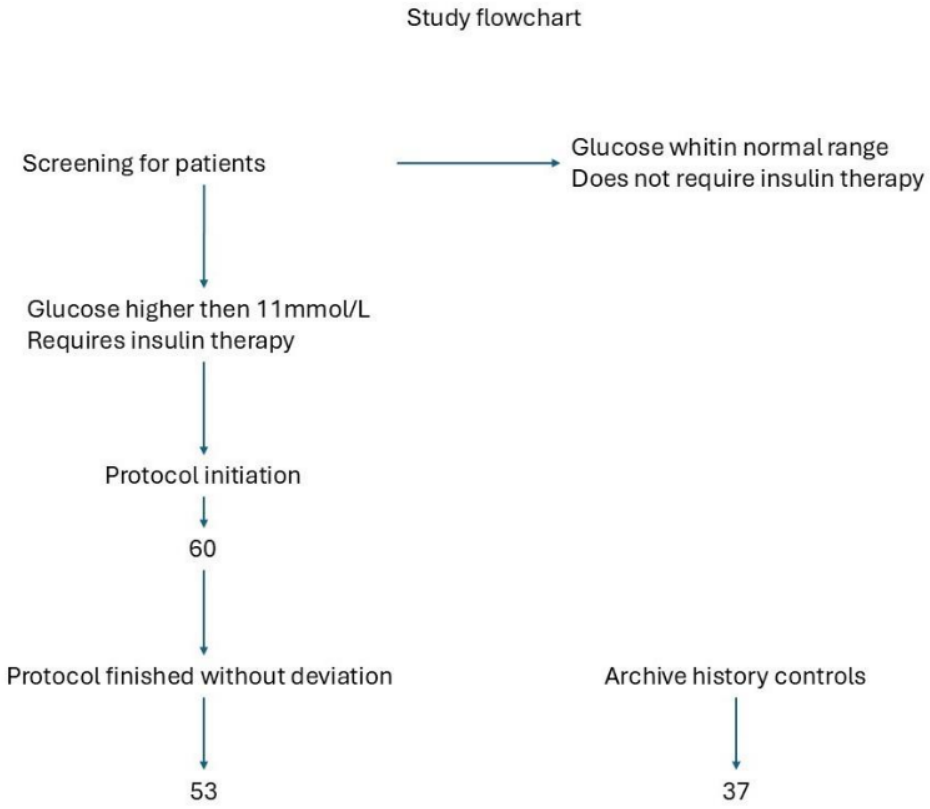
Figure 4. Difference in glycaemic penalty index

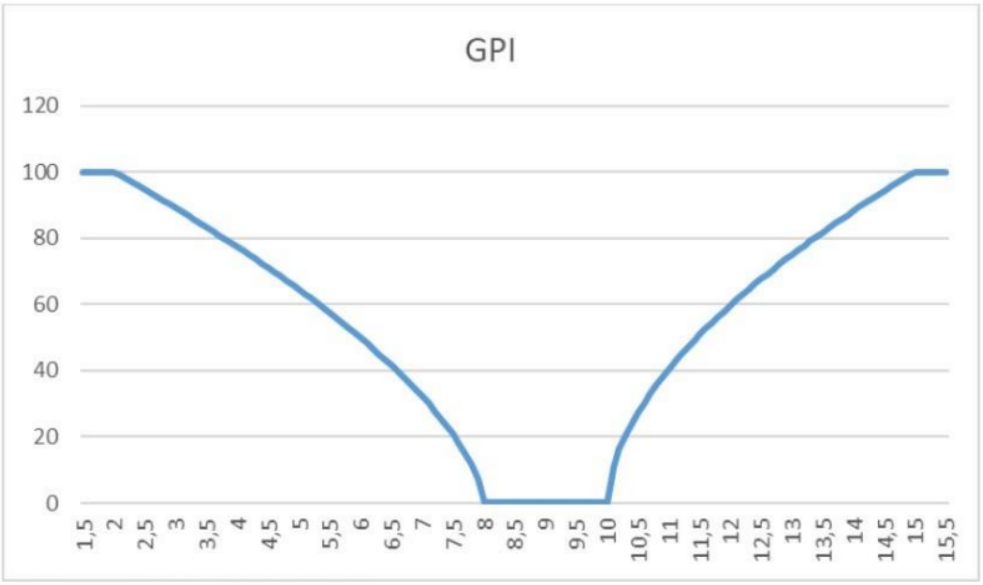
Figure 5. Difference in time in moderate to severe hypoglycaemia

Table 1. Table of results with mean and standard deviation for protocol and control group

	Protocol		Control		p
	M	SD	M	SD	
	N = 53		N = 37		
Mean BG	10,09	0,94	9,11	1,83	***0,005***
Median BG	9,68	0,92	9,08	1,87	*0,08*
Coeffitient of Glucose Variability	22,93	7,38	25,43	8,26	*0,089*
Glucose Fluctuation Index	1,71	0,51	1,75	0,89	*0,823*
Glucose Fluctuation Coeficient	16,86%	4,58%	18,76%	8,20%	*0,203*
modified Glycemic Penalty Index	22,15	9,91	33,67	11,87	***0,01***
Cumulative Time In Band	50,80%	15,04%	33,32%	16,75%	***0,01***
Time in Moderate to Severe Hypoglicemia in Hours (BG<4mmol/l)	0,21	0,84	1,70	2,76	***<0,001***
Proportion of Time in Moderate to Severe Hypoglicemia (BG<4mmol/l)	0,14%	0,62%	2,01%	4,82%	***<0,001***
Time Out of Band Hypoglicemia (BG<8mmol/l)	18,40	14,26	41,78	27,47	***<0,001***
Time Out of Band Hyperglicemia (BG>11mmol/l)	30,60	14,69	29,58	24,76	*0,473*
BG minimum	6,00	1,51	4,32	1,90	***<0,001***
BG maximum	16,74	3,26	15,36	4,51	*0,118*
Mean BG in 6 AM	9,88	1,29	8,83	2,10	***0,02***
Moderate to Severe Hypoglicemia (BG<4mmol/l) =YES	7,5%		51,4%		***<0,001***
APACHE II	19,89	5,2	20,16	5,75	*0,931*

Legend: M - mean, SD - standard deviation,


Study flowchart
Screening for patients
Glucose whitin normal range
Does not require insulin therapy
Glucose higher then 11mmol/L
Requires insulin therapy
Protocol initiation
60
Protocol finished without deviation
53
Archive history controls
37


GPI
120
100
80
60
40
20
0
1,5
2
2,5
3
3,5
4
4,5
5
5,5
6
6,5
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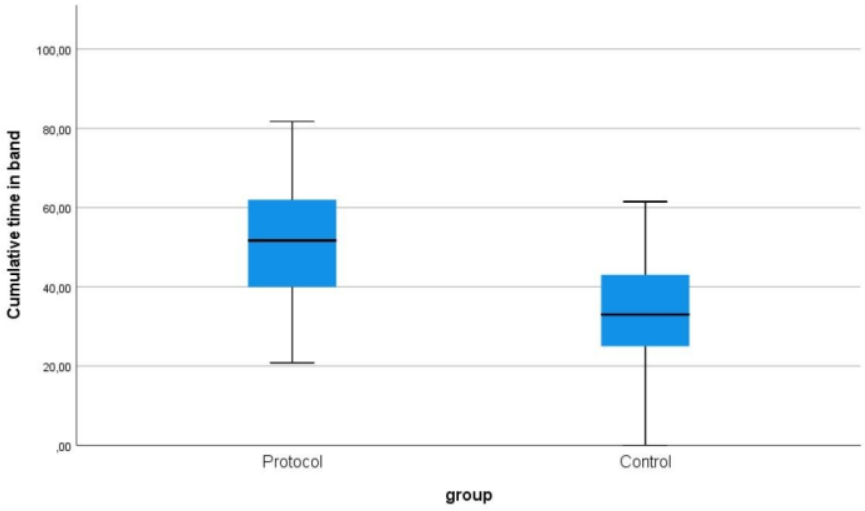
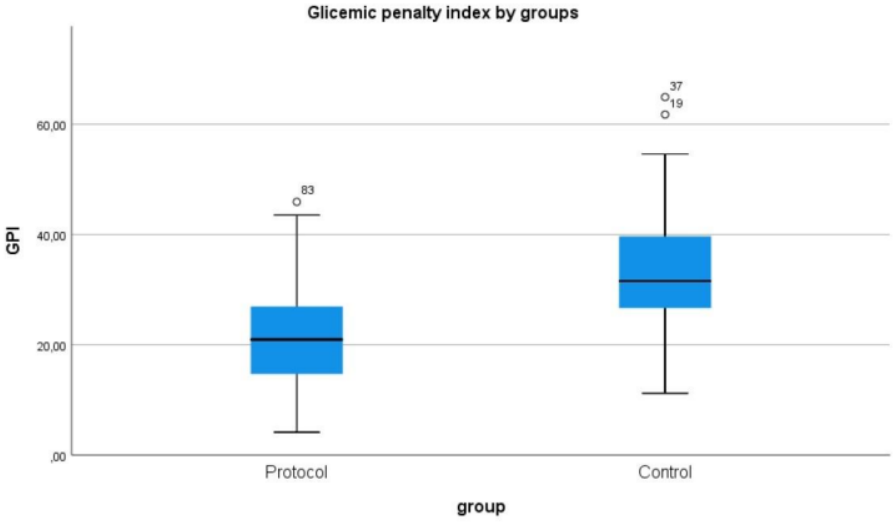
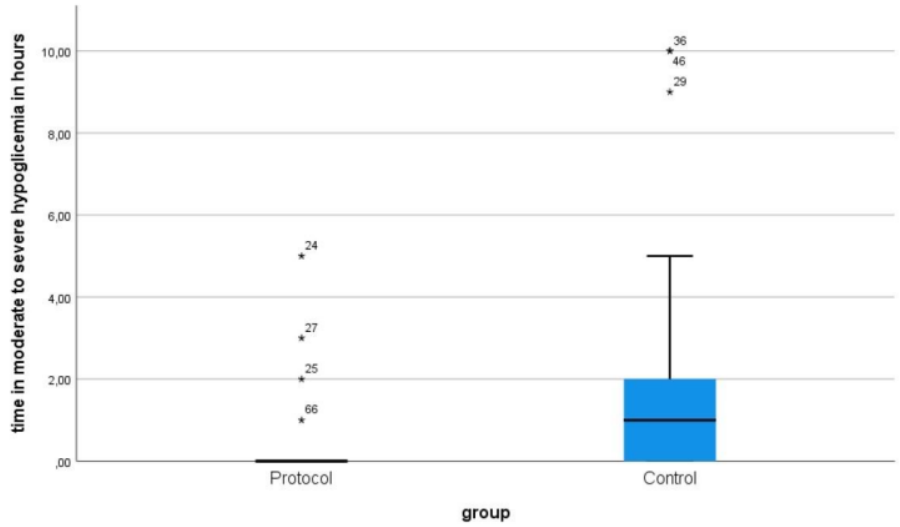

Cumulative time in band
100,00
80,00
60,00
40,00
20,00
,00
Protocol
Control
group


Glicemic penalty index by groups
GPI
60,00
40,00
20,00
,00
37
19
83
Protocol
Control
group


time in moderate to severe hypoglicemia in hours
10,00
8,00
6,00
4,00
2,00
,00
36
46
29
24
27
25
66
Protocol
Control
group