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Evaluation of Effectiveness and Safety of an ICU Insulin Infusion Protocol

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Abstract

Objective. To evaluate the efficacy, safety, and clinical outcomes of, and protocol deviations with the use of the Modified Yale Insulin Infusion Protocol (IIP) compared to usual/standard care in the local setting.

Methods. Chart review of patients admitted in two ICUs over a 2-year period was done. Patients eligible for intensive glycemic control were identified. Efficacy, safety and clinical outcomes were compared between the Modified Yale IIP and usual/standard care. Charts managed with the IIP were appraised for protocol deviations.

Results. Eighty-one patients met the inclusion criteria and 34.6% used the IIP. The IIP group achieved a lower mean blood glucose (185.1 vs 212.1 mg/dl, $p<0.05$). They reached normoglycemia (5 vs 12 hours, $p<0.05$) and target range of 140-180 mg/dl (8.3 vs 18.3 hours, $p<0.05$) earlier. Hypoglycemia was rare (median 0%) in both groups. No difference in mortality or morbidity was seen. Hospital (13.9 vs 8.1 days, $p<0.05$) and ICU stay (5.5 vs 3.0 days, $p<0.05$) were longer in the IIP group. A mean of 11 deviations per patient occurred, the majority of which were errors on insulin dose administered (66.6%).

Conclusion. The Modified Yale IIP is efficaceous, safe and yielded better glycemic profiles than usual care. Majority of protocol deviations were on the insulin dose administered.

Key words: insulin infusion protocol, hyperglycemia, intensive care unit, Filipino

INTRODUCTION

Hyperglycemia is common among the critically ill. There is clear evidence that hyperglycemia is correlated with poor clinical outcomes and glycemic control confers better prognosis.[1-8] The recommended strategy for glycemic control among the critically-ill is intravenous insulin adjusted based on a standardized protocol. The American Diabetes Association (ADA) recommends that insulin infusion protocols (IIP) be standardized in an institution. Its success is dependent on its adaptation to the hospital, adequate support from key local leaders, acceptance of the implementing staff and validation of the protocol.[9]

Numerous protocols in the medical, surgical and mixed ICUs have been published which showed efficacy and safety. One example is the Yale IIP which sets the glycemic target at 100-139 mg/dl. This protocol was used in a purely medical ICU. It demonstrated efficacy with 52% of blood glucoses (BG) within target and 66% of BGs within the clinically desirable range of 80-139 mg/dl. It is also safe, with a hypoglycemia rate of 0.3%. Nursing staff perception was favorable. More than 70% of nurses assessed the protocol as easy to use, effective and an improvement in the management of the critically ill.[10]

Efficacy, i.e., the ability of an IIP to achieve target glucose levels, and safety of an IIP are dependent on several factors. One is the intrinsic nature of the IIP which includes the way insulin drip rates are adjusted based on glucose changes. Another is how efficiently the protocol is implemented which depends on the skill of implementing staff, availability of resources and occurrence of protocol deviations.

In 2009, Josol, et al., modified the Yale IIP to target the new BG recommendations and adapt it to our hospital setting. The target BG was modified to 140-180 mg/dl to comply with the latest recommended glycemic targets for the critically-ill by the ADA.[9] During its initial observation, use of the protocol resulted in earlier time to achieve target BG range. More BG measurements were within acceptable levels compared with other methods of glucose control. Less hypoglycemic events were observed with the use of the IIP.[11]

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Since 2009, the Modified Yale IIP has been used in the medical and central ICUs of our hospital at the discretion of attending physicians. Two years after its conception, we aim to evaluate the effectiveness and usability of the Modified Yale IIP in our setting and compare it with usual care.

OBJECTIVES

The objective of our study is to evaluate the effectiveness of the Modified Yale IIP and compare it to usual/standard care in our setting. Specifically, we aim to evaluate the following: efficacy outcomes (mean BG achieved, mean/median BG achieved once normoglycemic, mean/median time in hours to normoglycemic and target ranges, and mean percentage of total BG in normoglycemia, target and off-target ranges), safety outcomes (median percentage of BG in hypoglycemia and severe hypoglycemia), and clinical outcomes (all-cause mortality, cardiovascular mortality, morbidity, and duration of ICU and hospital stay). We also aim to evaluate the frequency and types of protocol deviations committed in the performance of the IIP.

METHODOLOGY

Study Setting

The study was conducted in the Medical (MICU) and Central ICUs (CENICU) of the Philippine General Hospital. Our institution is a tertiary university and general hospital which caters to patients from the capital city and provinces nationwide. The MICU is a 12-bed capacity facility which serves purely medical charity/ service patients. The nurse-patient ratio is 1:3-4. There are approximately 400 admissions in the MICU annually. Most common reasons for admission are myocardial infarction, respiratory failure and sepsis.[12]

The CENICU is a 12-bed capacity facility with 10 beds allotted for self-pay patients and 2 beds for charity/service patients. The nurse-patient ratio is 1:2-3 . There are also approximately 400 admissions in the CENICU annually. Cases are mixed medical & surgical. The most common reasons for admission are respiratory failure and postoperative care for neurosurgical and cardiac surgery cases.[13]

In these ICUs, glycemic management is not standardized. Strategies for glycemic control are at the discretion of the attending physicians.

Study Population

All charts of patients admitted at the MICU and CENICU in the period of January 2010 to December 2011 were ordered for retrieval. Patients eligible for intensive glycemic control via an intravenous IIP were identified. Indications included (1) BG > 180 mg/dl on two consecutive determinations, (2) on *nil per os* or parenteral nutrition and (3) any of the following: critical care illness, hemodynamic instability, perioperative care, type 1 diabetes, and high dose steroids. Patients with diabetic ketoacidosis or hyperosmolar hyperglycemic state were excluded. Method of glycemic control was identified by review of doctors' orders. Patients who were managed suboptimally (e.g., went home against advice, advanced directives of "Do not Resuscitate" (DNR), refused interventions) were excluded from the control group and in the analysis of clinical outcomes for the Modified Yale Group.

The Modified Yale Insulin Infusion Protocol

The Yale IIP was created by Goldberg, et al., for the Yale University School of Medicine in 2004.[10] It was originally designed to target BG of 100-139 mg/dl. This protocol was chosen by Josol et al., because of its demonstrated efficacy, safety, ease of use and it was tested in a similar population to our ICU.[11]

Modifications of the Yale IIP including changing the target to 140-180 mg/dl. The threshold for hypoglycemia correction was also revised. Insulin infusion is withheld once BG approaches <100 mg/dl in contrast to the original Yale IIP where the threshold is at ≤74 mg/d. These modifications were done to comply with latest recommended glycemic targets for the critically ill by the ADA and to minimize the risk for hypoglycemia.[9]

The Modified Yale IIP was introduced in our institution in 2009. It was discussed in several Department of Medicine conferences with consultants and house staff but there was no formal training. The IIP was taught to ICU nurses by an Endocrine consultant in several training sessions. Presently, it is not part of the standard ICU care for diabetics and is being used at the discretion of physicians.

Study Design

The study is a retrospective cohort. Chart review of the specified study population was done. Method of glycemic control was extracted via review of doctors orders on charts by the primary investigator. Charts with explicit written orders to start the Modified Yale Protocol were identified. The control group was composed of patient charts meeting the inclusion criteria but with explicit orders other than the Modified Yale protocol which included sliding scale insulin, subcutaneous insulin, non-standardized intravenous insulin infusions among others.

Demographic and clinical data of patients were extracted from charts. Glucose measurements were extracted from standard vital monitoring sheets and doctors' and nurses' notes. These forms were similar regardless of method of glycemic control. Blood glucose in the first 72 hours on intensive glucose control were extracted to determine the efficacy and safety outcomes. Clinical outcomes were

identified. All data were entered into a data collection form.

Outcomes were compared between the two groups. Type and frequency of protocol deviations were identified in charts which employed the Modified Yale IIP. In the IIP group, a subset analysis of all outcomes was done among patients with at most 50% protocol deviations which is the threshold set by the investigators as an acceptable number of deviations.

Missing chart entries on BG readings were interpreted as failure to take BG levels at the assigned time and considered protocol deviations. Charts missing entire glucose monitoring sheets or pages with the initial orders of glycemic management strategies were excluded from the analysis.

Outcome Measures

Outcomes were categorized into efficacy, safety and clinical events. Efficacy outcomes included the following: mean BG achieved, median BG achieved once normoglycemic (BG 70-180 mg/dl), mean/median time in hours to normoglycemia and target range (140-180 mg/dl), and mean percentage of total measurements in normoglycemia, target and off-target ranges (BG <70, >180 mg/dl). Safety outcomes included median percentage of BG in hypoglycemia and severe hypoglycemia. Hypoglycemia was defined as recorded BG measurements less than 70 mg/dl while severe hypoglycemia was defined as recorded BG measurements less than 40 mg/dl.

Clinical outcomes included all-cause mortality, cardiovascular mortality (acute coronary syndrome, cerebrovascular accident, arrhythmia), morbidity in the ICU (new cardiovascular event; need for initiation of mechanical ventilation; need for initiation, reinitiation or addition of vasopressors; new infection; new renal dysfunction defined as initial serum creatinine 1.5 mg/dl or lower which increased to above 2.5 mg/dl or increase by at least two-fold from baseline; need for transfusion of packed RBC, excluding patients admitted for gastrointestinal bleeding), duration of ICU and hospital stay.

Protocol deviations were classified into three: timing of CBG monitoring (obtained ± 15 minutes of specified time), insulin dose administered and errors on hypoglycemia correction (failure to stop the drip, give D50 or restart insulin drip rate at proper dose).

Statistical Analysis

To achieve 95% confidence and 80% power in detecting a significant difference between two independent means assuming 73.84% ± 17.68% is the mean percentage of BG within normoglycemic range in the IIP group and 51.74% ± 25.03% for the control group based on the study of Josol et al.,[11] it was estimated that a minimum sample size of 17 cases were necessary in each group.

Baseline characteristics were summarized using frequencies and percentages for categorical variables and mean/median and standard deviation for continuous variables. Chi-square test for categorical variables and T-test or Mann-Whitney Ranksum test for continuous variables were used to analyze baseline characteristics and BG measurements for efficacy and safety outcomes. Clinical events outcomes were compared using Chi-square test for mortality rate and T-test or Mann-Whitney Ranksum test for length of hospital stay and ICU stay. All statistical tests were considered significant if p-value is less than 5%.

Ethical Considerations

The study protocol was reviewed and approved by the Technical Review Board (TRB) of the Department of Medicine and the UP Manila Research Ethics Board (UPMREB).

RESULTS

A total of 81 patients among the charts retrieved met the inclusion criteria. Twenty eight patients (34.6%) were managed using the Modified Yale IIP. Figure 1 shows the composition of the study cohort.

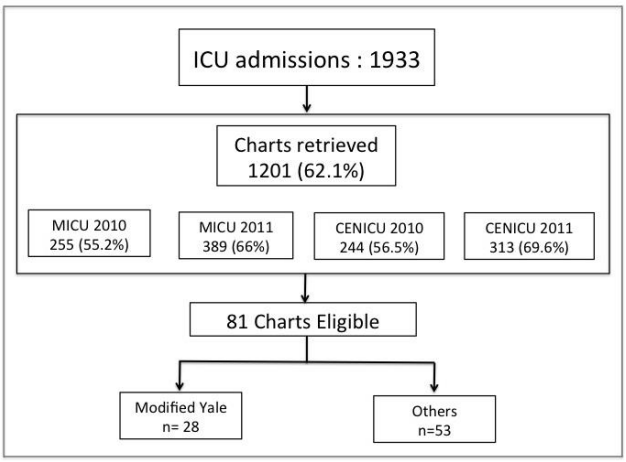

Figure 1. Composition of the Study Cohort

For the control group, 73.6% of patients were managed using sliding scale subcutaneous insulin. In 6 charts (11.3%), intravenous insulin adjusted via a non-standardized protocol was used. A combination of intravenous and intermittent subcutaneous insulin was also used in 5 charts (9.4%). Majority (65.3%) of BG determination and insulin interventions were done every 4 hours.

Baseline characteristics of the two groups were comparable, except for a greater proportion of diabetes

and sepsis in the IIP group. Despite the disparity, initial blood glucose measurements were similar. APACHE II scores were 24 and 21 in the IIP and control groups respectively and were statistically similar. Both levels denote severe illness with a risk for mortality of at least 54.4%.[14] The most common admitting diagnoses in both groups were shock, diabetes and sepsis. Majority of patients were on mechanical ventilation, vasopressor support and *nil per os* (Table 1).

Table 1. Baseline characteristics of study population, N= 81

	Modified Yale IIP Group (n=28)	Control Group (n=53)	p-value
Demographics			
Age (years, mean ± SD)	57.1 ± 12.6	58.3 ± 13.7	0.69
Gender			0.50
Male (n, %)	11 (39.3%)	25 (47.2%)	
Female (n, %)	17 (60.7%)	28 (52.8%)	
Severity of Illness (APACHE II, mean ± SD)	24.0 ± 8.4	21.4 ± 8.7	0.23
Location (n, %)			
MICU	13 (48.1%)	20 (38.5%)	0.41
CENICU	14 (51.9%)	32 (61.5%)	
Diagnoses on admission (n,%)			
Shock	21 (75.0%)	36 (67.9%)	0.51
Septic	7 (25.0%)	10 (18.9%)	0.52
Cardiogenic	4 (14.3%)	12 (22.6%)	0.37
Hypovolemic	1 (3.6%)	2 (3.8%)	1.00
Multifactorial	8 (28.6%)	8 (15.1%)	0.15
Acute Respiratory Failure	11 (39.3%)	12 (22.6%)	0.11
Sepsis	20 (71.4%)	23 (43.4%)	0.02*
Acute Coronary Syndrome	9 (32.1%)	16 (30.2%)	0.86
Congestive heart failure	4 (14.3%)	9 (17.0%)	0.75
Arrhythmia	0 (0.0%)	6 (11.3%)	0.09
Post cardiopulmonary arrest	6 (21.4%)	6 (11.3%)	0.22
Cerebrovascular event	2 (7.1%)	8 (15.1%)	0.30
Diabetes	19 (67.9%)	19 (35.8%)	0.01*
Gastrointestinal bleeding	10 (35.7%)	14 (26.4%)	0.38
Acute Kidney Injury	8 (28.6%)	17 (32.1%)	0.75
Chronic Kidney Disease	7 (25.0%)	6 (11.3%)	0.11
Post-surgical	5 (17.9%)	10 (18.9%)	0.91
CABG	0 (0.0%)	3 (5.7%)	0.55
Neurosurgical	2 (7.1%)	4 (7.5%)	1.00
Others	3 (10.7%)	3 (5.7%)	0.41
Therapeutic Modalities (n,%)			
Mechanical Ventilation	22 (78.6%)	44 (83.0%)	0.62
Inotropes/vasopressors	21 (75.0%)	37 (69.8%)	0.62
Steroids	10 (35.7%)	9 (17.0%)	0.06
TPN	5 (17.9%)	3 (5.7%)	0.08
NPO	26 (92.9%)	53 (100%)	0.12
Mean capillary blood glucose at start of intervention (mg/dl, mean ± s.d.)	243.6 ± 106.3(	245.1 ± 63.95	0.95
Duration of the protocol (hours, mean ± s.d.)	30.7 ± 18.4	33.8 ± 21.2	0.52

** Significant difference at α = 0.05*

Efficacy and Safety Outcomes

Patients on the Modified Yale IIP achieved a significantly lower mean BG compared with the control group (185.1 vs 212.1 mg/dl, p=<0.05) during the entire observation period. However, once normoglycemia was reached, the median BG were already similar for both groups (158.1 vs 159.6 mg/dl, p=0.14). Time to reach normoglycemia (5 vs 12 hours, p<0.05) and target BG range of 140-180 mg/dl (8.3 vs 18.3 hours, p<0.05) were shorter for the IIP group. There was a significantly higher mean proportion of normal BG in the IIP group. Mean proportion of BG within target range was similar for both groups. A greater number of patients were able to achieve normoglycemia in the IIP group but the proportion of patients who were able to reach target BG was similar. Hypoglycemia was rare for both methods of glycemic control. Table 2 summarizes the efficacy and safety outcomes.

Table 2. Comparison of efficacy and safety outcomes between modified Yale IIP and control group, N= 81

	Modified Yale IIP (n=28)	Control Group (n=53)	p-value
Efficacy Outcomes			
Blood glucose level (mg/dl)			
All measurements (mean ± s.d.)	185.1 ± 51.6	212.1 ± 54.4;	0.034*
Once normoglycemia achieved (median)	158.1	159.6	0.140
Time to (hours)			
Target (mean + s.d.)	8.3 ± 9.7	18.3 ± 11.6	0.001*
normoglycemia (median)	5.0	12.0	0.001*
Mean % of total measurements in	**(%)**		
normoglycemia (mean + s.d.)	57.4 ± 29.8	32.9 ± 28.7;	0.001*
target (mean + s.d.)	21.9 ± 14.5;	17.9 ± 18.5;	0.322
Number of patients (n,%)			
achieved normoglycemia	28 (100.0%)	39 (73.6%)	0.003*
achieved target range	24 (85.7%)	36 (67.9%)	0.082
Safety Outcomes			
% of Blood glucose in			
hypoglycemia (median)	.0	.0	0.889
severe hypoglycemia (median)	.0	.0	0.310

Significant difference at α = 0.05
Definitions :
Normoglycemia : 70-180 mg/dl; target : 140-180 mg/dl; off-target : <70, >180 mg/dl
Hypoglycemia : < 70 mg/dl; severe hypoglycemia : <40 mg/dl

Clinical Outcomes

Four patients in the IIP group were excluded from the analysis for clinical outcomes due to submaximal treatment. One patient had advanced directives orders ("Do not resuscitate") and 3 went home against medical advice. There were no significant differences noted in all-cause mortality, cardiovascular mortality and occurrence of any morbidity between the two groups. Among the specific complications, only the need for transfusion of packed red cells was seen to be significantly higher in the IIP group. The IIP group had a significantly longer ICU and hospital stay (Table 3).

Protocol Deviations

All charts (28) which employed the Modified Yale IIP were examined for protocol deviations. Of the 518 capillary BG determinations, 296 episodes (57.1%) of deviations were identified. Majority (66.9%) were errors on insulin dose administered (Table 4). Majority of patients had deviations in more than one category with 35.7% in all three, 46.4% in two and 17.9% in one category. All patients had at least one deviation. On a per patient basis, a mean of 11 episodes of deviations occurred. Four patients had more than 50% deviations in at least one category. Subgroup analysis of patients with acceptable protocol deviations (<50%) yielded slight improvement in the efficacy parameters. Comparison with the control group yielded identical comparisons of efficacy and safety (Table 5).

Table 3. Comparison of clinical outcomes between modified Yale IIP and control group, N= 77

	Modified Yale IIP Group (n=24)	Control Group (n=53)	p-value
All cause Mortality (n,%)	15 (62.5%)	36 (69.2%)	0.56
Cardiovascular mortality (n, %)	5 (20.8%)	14 (27.5%)	0.54
Morbidity (n,%)	17 (70.8%)	32 (61.5%)	0.43
CP arrest, revived	4 (16.7%)	5 (9.4%)	0.36
New cardiovascular event	2 (8.3%)	2 (3.8%)	0.59
Initiation of mechanical ventilation	1 (4.2%)	4 (7.5%)	1.00
Initiation of vasopressors/ inotropic support	4 (16.7%)	16 (30.2%)	0.21
Addition of vasopressors	8 (33.3%)	9 (17.0%)	0.11
New infection	8 (33.3%)	12 (22.6%)	0.32
New Renal dysfunction	2 (8.3%)	3 (5.7%)	0.64
Need for transfusion of packed RBC	10 (41.7%)	11 (20.8%)	0.05
Arrhythmia	2 (8.7%)	4 (7.5%)	1.00
ICU stay (days, median)	5.5	3.0	0.01*
Hospital stay (days, median)	13.9	8.1	0.02*

Significant difference at α = 0.05
** Patients with submaximal treatment, e.g., advanced directives, home against advice, etc., were excluded in the analysis.*

Table 4. Summary of protocol deviations with the use of the modified Yale IIP

Category of deviation	Proportion from total deviations n=296	Episodes per patient (mean, range)	Mean proportion per patient (episodes/total CBGs per patient)
Timing of CBG determination	24 %	2.53 (0,16)	12.9%
Insulin dose administered	66.9 %	7.07 (1,24)	30.7%
Hypoglycemia protocol	9.1 %	0.96 (0,5)	32.1%*

- (number of deviations/number of episodes with need for hypoglycemia protocol per patient) x 100

Table 5. Comparison of efficacy and safety outcomes between all patients in the modified Yale IIP, those with acceptable protocol deviations (PD) and with the control group

Efficacy Outcomes	Modified Yale IIP Group		Modified Yale IIP with Acceptable PD* vs Control group
	All (n=28)	Acceptable PD* (n=24)	p-value
Blood glucose level (mg/dl)			
All measurements (mean ± s.d.)	185.1 ± 51.6	182.0 ± 49.2	.023
Once normoglycemia achieved (median)	158.1	153.1	.087
Time to (hours)			
Target (mean + s.d.)	8.3 ± 9.7	8.3 ± 9.7	.001
normoglycemia (median)	5.0	4.5	.000
% of total measurements (%)			
normoglycemia (mean + s.d.)	57.4 ± 29.8	59.8 ± 28.3	.000
target (mean + s.d.)	21.9 ± 14.5	23.5 ± 14.8	.202
Number of patients (n,%)			
achieved normoglycemia	28 (100%)	24 (100.0%)	.005
achieved target range	24 (85.7%)	21 (87.5%)	.070
Safety Outcomes			
% of Blood glucose in			
hypoglycemia (median)	0	.0	0.928
severe hypoglycemia (median)	0	.0	0.348

** Acceptable PD is defined as less than 50% of BG measurements with protocol deviation*
Significant difference at α = 0.05

DISCUSSION

In our institution, glycemic management of the critically ill is not standardized. The majority of physicians still use sliding scale subcutaneous insulin. In 2009, the Modified Yale IIP was introduced in an effort to improve patient care and adhere to current recommendations on ICU glycemic management. Our study aimed to evaluate the IIP as it is being implemented in actual practice.

Our study was able to show that use of the Modified Yale IIP is efficaceous and safe. The IIP is efficaceous because the majority of patients were able to reach acceptable glucose levels in a reasonable time. Normoglycemia and target ranges were achieved at 5 and 8.4 hours respectively. The majority (58.3%) of BGs were within normoglycemic range. Once normoglycemia was achieved, the mean BG was 155.2 mg/dl The IIP is safe because hypoglycemia was rare with a median of zero events.

Compared to other methods, the Modified Yale IIP resulted in more favorable efficacy outcomes. More patients achieved normoglycemic glucose range. A lower mean BG was reached. Target and normoglycemic levels were reached faster. Outcomes were in favor of the IIP despite a higher proportion of diabetes and sepsis, factors known to perpetuate hyperglycemia, in the IIP group.

However, proportion of BG achieving target range was similar. These results are comparable with the initial evaluation done by Josol, et al., in 2009. In this study, the Modified Yale IIP was employed in 50 ICU patients and compared with 50 patients managed differently. Similar to our review, the IIP demonstrated shorter median time to normoglycemia at 4 hours versus 12 hours for control group. The IIP group also had a higher proportion of BG in the normoglycemic range at 73.8% compared to 51.7% for the control group. Hypoglycemia was minimal at 0.6% for the IIP group.[11]

There are some differences noted between the two studies. In the study of Josol, the mean BG was 161 mg/dl for the IIP group. This is lower than what we achieved which is at 185.1 mg/dl. Furthermore, the first study achieved a higher proportion of BG in the normoglycemic (73.8%) and target (30%) ranges. One possible reason for the disparity could be the differences in the characteristics of the two cohorts. Our patients had more severe illness as shown by a higher mean Apache II score, more patients on ventilatory and vasopressor support, with diabetes and on steroids. These factors may make glycemic control more difficult. A second reason may be the settings of the study. Unlike the past review which is in ideal set-up, our current study is a "real-world" setting with confounding factors like logistics and proficiency of implementing staff influencing outcomes.

The Yale IIP was also employed and modified in other centers.[15-18] In the study of Tamaki, et al., conducted in Japan, a cohort of 40 cardiac surgery patients were compared to a historical cohort of 35 patients. A significantly higher proportion of target BG (78% vs 57%) was demonstrated in the IIP group. Time to target was also shorter for the IIP group (3.1 vs 5.0 hours).[15] These favorable results were likewise reported in centers in Brazil, Portugal and the US.[16-18]

In our study, a substantial number of protocol deviations occurred. The most frequent deviation was on improper insulin dose adjustment followed by improper timing of BG checks. Despite the prevalence of protocol deviations, the IIP group still resulted in better glycemic outcomes. In a survey on the experience of our medical staff on the use of the Modified Yale IIP, our nurses noted that the most difficult and error-prone tasks were initiating the insulin drip followed by adjusting the insulin drip rate. The nurses explained that the multistep instruction of the protocol can be confusing and time-consuming.[19] Simplicity and clarity are, therefore, desirable attributes of a protocol.[20] The attitude and skill of the implementing staff also likely affect the occurrence of protocol deviations. Clear understanding of the IIP's promised benefits will lead to an improved attitude despite the increase in workload.[21] It is of utmost importance to improve the skill of implementing hospital staff to preserve the integrity of the protocol and derive the best benefit. Frequent and periodic training, streamlining and feedback should be done.

Suboptimal compliance to the IIP has been similarly reported. In the study of Malasker, et al., 75% of all BG measurements were associated with protocol deviations. Majority (57%) of deviations were improper timing of BG checks followed by 38% on erroneous insulin dose adjustment.[22] A similar situation was seen in Brigham and Women's Hospital as reported by Cyrus et al., where 31.2% of insulin adjustments were incorrect and 55.2% of glucose checks were done beyond 10 minutes of the prescribed time. [23]

Comparison of mortality and morbidity showed little differences in our study apart from an increase in blood transfusion in the IIP group. These results are consistent with the report of Josol.[11] A similar study by Krinsley which compared glycemic and clinical outcomes before and after institution of an ICU glucose management protocol reported otherwise. In this study of 1600 patients, the use of an IIP resulted in a 29.3% decrease in mortality, 75% decrease in new renal insufficiency and 18.7% decrease in blood transfusion. Perhaps, the disparity is due to the small number of patients in whom the IIP was used in our study, such that we did not achieve statistical power to detect the difference. Another reason could be the differences in BG achieved. In our study, the mean BG after use of the Modified Yale IIP was 182.3 mg/dl which is higher than that achieved by the group of Krinsley at 130.7 mg/dl. [24]

It is difficult to determine why patients in the IIP group in our study had a longer ICU and hospital day stay. This is in contrast to the results of Krinsley which showed a 10.8% decrease in length of hospital stay.[24] One possible explanation may be the higher proportion of sepsis in the IIP group. Presence of sepsis and infection in the 1st 24 hours in the ICU has been shown to be associated with longer ICU and hospital stay.[25,26]

Our study has several limitations. First, it is a retrospective study which assumes that the two groups compared are similar. The two groups are reasonably comparable, the majority of the demographic characteristics are statistically similar. Two variables, the percentage of patients with sepsis and diabetes, were cause for heterogeneity. However, despite a higher proportion of these factors, glycemic outcomes were still better in the IIP group. Since the IIP was used at the discretion of physicians, level of care and conscientiousness in achieving glycemic targets by the medical staff may confound the comparison of outcomes between the IIP and control groups. However, we can still attribute benefit to the IIP because, even without comparing it to the control group, it yielded good outcomes. Other variables which may affect outcomes such as hospital policies, nursing staff or logistics were

assumed to be similar since the observation period is the same.

Secondly, occurrence of hypoglycemia was based solely on BG entries in monitoring sheets and notes. Episodes of hypoglycemia may have been unrecognized by patients or failed to have been recorded by health care providers leading to underreporting of these events.

Thirdly, measurement of BG was via capillary blood glucose. In light of the high proportion of patients in shock, these values may not be entirely accurate since disparity can occur with peripheral vasoconstriction and endothelial dysfunction. Capillary blood glucose, however, is more practical and is the method used in usual clinical practice. Measurement of arterial BG will entail either an indwelling catheter or frequent phlebotomy which is not usual in our set-up. Furthermore, the glucose meters were the standard machines used in the ICUs at the time of observation but we cannot ascertain if these were changed during the two years of observation. Lastly, as was previously stated, this study was not statistically powered to detect a difference in clinical outcomes such as mortality and morbidity.

We have several recommendations based on the results of this study. First, improve the process of implementing the Modified Yale IIP by wider dissemination of its relevance, periodic training of the ICU staff on carrying out the protocol, provide avenues for consultation and streamlining of the protocol and secure institutional support. We also recommend further investigations on the efficacy, safety and effect on duration of ICU and hospital stay of the Modified Yale IIP through prospective studies and, perhaps, compare it with other standardized protocols.

CONCLUSION

The Modified Yale IIP is efficaceous and safe for ICU patients. Compared with other methods of glycemic control, use of the protocol yielded better glycemic profiles. A significant amount of protocol deviations occurred, with the most common being errors in insulin dose adjustment.

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APPENDIX. MODIFIED YALE INSULIN INFUSION PROTOCOL (IIP)

INITIATING AN INSULIN INFUSION

1. INSULIN INFUSION: Mix 1 unit Human Regular Insulin per 1 cc 0.9% NaCl. Administer in infusion pump (in increments of 1 unit/h).
2. PRIMING: Flush 50cc of infusion through all IV tubing before infusion begins (to saturate the insulin binding sites in the tubing).
3. THRESHOLD: Start IV insulin if BG is **> 180 mg/dl.**
4. TARGET BLOOD GLUCOSE LEVELS: **140-180 mg/dL**
5. BOLUS & INITIAL INSULIN INFUSION RATE: If initial BG >180mg/dl but <300 mg/dl, divide by 100, then round to the nearest 1 unit for initial drip rate, (don't give IV bolus insulin). If initial BG is ≥300 mg/dl, divide by 100 for bolus and initial drip rate.

BLOOD GLUCOSE MONITORING

1. Check blood glucose hourly until stable (3 consecutive values within target range). In hypotensive patients, capillary blood glucose (i.e., fingersticks) may be inaccurate and obtaining blood sample from an indwelling vascular catheter may be preferable.
2. Then check blood glucose q 2 hours; once stable x 12-24 hrs. Blood glucose checks can then be spaced to q 4 hrs. IF:
   a. no significant change in clinical condition AND
   b. no significant change in nutritional intake
3. If any of the following occur, consider the temporary resumption of hourly blood glucose monitoring, until blood glucose is again stable (2-3 consecutive BG values within target range):
   a. any change in insulin infusion rate (i.e. blood glucose out of target range)
   b. significant changes in clinical condition
   c. initiation or cessation of pressor or steroid therapy
   d. initiation or cessation of renal replacement therapy (dialysis, CVVH, etc.)
   e. initiation, cessation, or rate change of nutritional support (TPN, PPN, tube feedings, etc.)

CHANGING THE INSULIN INFUSION RATE

If BG <50 mg/dL:

D/C INSULIN INFUSION:

Give 1 amp (25 g) D50 IV; recheck blood glucose q 15 minutes.

- When blood glucose ≥ 100 mg/dL, wait 1 hour, recheck BG. If still ≥ 100 mg/dL, restart infusion at 50% of most recent rate.

If BG 50-69 mg/dL:

D/C INSULIN INFUSION:

If symptomatic (or unable to assess), give 1 amp (25 g) D50 IV; recheck blood glucose q 15 mins.

If asymptomatic, give ½ amp (12.5 g) D50 IV; recheck BG q 30 mins.

- When BG ≥ 100 mg/dl, wait 1 hour, recheck BG. If still ≥ 100 mg/dl, restart infusion at 75% of most recent rate (round off to the nearest 1 unit)

If BG 70-99 mg/dl:

D/C INSULIN INFUSION FOR 30 mins.

If repeat CBG ≥ 100 mg/dl, restart insulin infusion at 75% of most recent rate (round off to the nearest 1 unit)

If repeat CBG is still <100 mg/dl, re-chek CBG after 1 hour., resume insulin infusion only at 75% of most recent rate once repeat CBG is ≥ 100 mg/dl (round off to the nearest 1 unit)

If BG ≥100

STEP 1: Determine CURRENT BG & identify column in table

BG 100-139 mg/dl	BG 140-179 mg/dl	BG 180-249 mg/dl	BG ≥ 250 mg/dl

STEP 2: Determine the RATE OF CHANGE from prior BG level- identifies a CELL in the table- Then move right for the INSTRUCTIONS:
(Note: If the last BG was measured 2-4 hrs. before the current BG, calculate the hourly rate of change.)

BG 100-139 mg/dl	BG 140-179 mg/dl	BG 180-249 mg/dl	BG ≥ 250 mg/dl	Instructions
		BG ↑ by >40 mg/dl/hr	BG ↑	↑ Infusion by "2Δ"
	BG ↑ by >20 mg/dl/h	BG ↑ by 1-40mg/dl/h or BG unchanged	BG unchanged or BG ↓ by 1-40 mg/dl/h	↑ Infusion by "Δ"
BG ↑	BG ↑ by 1-20 mg/dl/h, BG UNCHANGED, OR BG ↓ 1-20 mg/dl/h	BG ↓ by 1-40 mg/dl/h	BG ↓ by 41-80 mg/dl/h	No infusion change
BG UNCHANGED OR BG ↓ by 1-20 mg/dl/h	BG ↓ by 21-40 mg/dl/h	BG ↓ by 41-80 mg/dl/h	BG ↓ by 81-120 mg/dl/h	↓ Infusion by "Δ"
BG ↓ by > 20 mg/dl/h ***see below**	BG ↓ by >40 mg/dl/h	BG ↓ by >80 mg/dl/h	BG ↓ by >120 mg/dl/h	Hold X 30 mins., then ↓ Infusion by "2Δ"

*D/C INSULIN INFUSION, check CBG after 30 mins., when BG is ≥100 mg/dl, restart infusion at 75% of most recent rate

CHANGES IN INFUSION RATE ("Δ") are determined by the current rate:

Current Rate (units/hr)	Δ = rate change (units/hr)	2Δ= 2x rate change (units/hr)
<3	**0.5**	**1**
3-6	**1**	**2**
6.5 – 9.5	**1.5**	**3**
10-14.5	**2**	**4**
15-19.5	**3**	**6**
20-24.5	**4**	**8**
≥25	**≥5**	**10 (consult MD)**