

# Comparison of Two Protocols in the Management of Glucocorticoid-induced Hyperglycemia among Hospitalized Patients

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## Abstract

**Context:** There is limited literature focusing on the management of glucocorticoid-induced hyperglycemia (GCIH). **Aims:** The primary objective was to compare the mean blood glucose between the experimental group (new protocol) and the control group (standard protocol) in the management of GCIH. The secondary objective was to compare other parameters of glycemic efficacy, variability, and safety parameters. **Methods:** This was a randomized, open-labeled, parallel arm trial. Adult patients who were given glucocorticoid (minimum dose equivalent to prednisolone 10 mg) in the past 24 h and had 2 h postmeal plasma glucose  $\geq 200$  mg/dl were included in the study. Patients randomized to control group received standard basal-bolus insulin. In the experimental group, a “correctional insulin” matching the glycemic profile of the glucocorticoid administered was provided with or without “background” basal-bolus insulin. The parameters of glycemic efficacy, variability, and safety were compared.  $P < 0.05$  was considered statistically significant. **Results:** Data of 67 patients included in the study were analyzed, of which 33 patients were in the experimental group and 34 patients in the control group. The mean blood glucose in the experimental and the control group was  $170.32 \pm 33.46$  mg/dl and  $221.05 \pm 49.72$ , respectively ( $P = 0.0001$ ). The parameters for glycemic variability were all significantly lower in patients in the experimental group. The hypoglycemia event rate was low in both the groups. **Conclusion:** When compared to the standard basal-bolus insulin protocol, the new protocol showed lower mean blood glucose and lower glycemic variability.

**Keywords:** Glucocorticoid-induced hyperglycemia, steroid-induced diabetes, steroid-induced hyperglycemia

## INTRODUCTION

Glucocorticoids are popular therapeutic agents in clinical medicine. One of the major side effects of glucocorticoids is to cause an increase of blood glucose (hyperglycemia). The effect of glucocorticoids on glucose metabolism was first described by Ingle<sup>[1]</sup> in 1941.

Management of glucocorticoid-induced hyperglycemia (GCIH) among hospitalized patients is a challenge. A study revealed that 64% of indoor patients who received glucocorticoids equivalent to prednisolone  $\geq 40$  mg developed hyperglycemia.<sup>[2]</sup> Hyperglycemia induced by glucocorticoids has an impact on mortality and morbidity. Studies in patients with hematological malignancies who develop GCIH have shown increased hospital stay, mortality, sepsis, and shorter periods of remission.<sup>[3]</sup>

Based on our review of literature and understanding of the pharmacokinetics and pharmacodynamics of glucocorticoids, we developed a new protocol for the management of GCIH in hospitalized patients. The new protocol included the use of a “correctional insulin” which matches the glycemic profile of the glucocorticoid administered with or without “background” basal-bolus insulin. The dose of correctional insulin was based on the dose of the administered glucocorticoid and weight of the patient.

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The primary aim of the study was to compare the mean blood glucose between the experimental group (new protocol) and the control group (standard basal-bolus insulin protocol) in the management of GCIH in hospitalized patients.

The secondary objective was to compare other parameters of glycemic efficacy between the two groups, glycemic variability, and safety between the two groups.

## METHODS

This study was conducted at a single tertiary care institution in New Delhi. This was a randomized, open-labeled, parallel arm trial. Permission for the study was granted by the Institutional Ethics Committee on August 4, 2014. The study was conducted from August 2014 to April 2016.

We used the data from the pilot study conducted by Seggelke *et al.*<sup>[4]</sup> for calculating our sample size. The calculated sample size was 23 for each group (total of 46). However, to improve the power of the study, we had decided to enroll 92 patients (double the calculated sample size). This gave our study a power of 99% with an alpha error of 0.05.

Patients screened for eligibility to be included in the study were nonpregnant patients of ages 18 years and above, with or without diabetes mellitus (Type 1, Type 2, or other forms of diabetes mellitus), who were admitted to the nonintensive care unit of our hospital from August 2014 to April 2016. A screening was conducted to find the patients who were given systemic glucocorticoid (oral or parenteral) for any indication (minimum dose equivalent to prednisolone dose of 10 mg) in the past 24 h.

Plasma glucose was checked 2 h after lunch and 2 h after dinner within 24–48 h of the patients receiving the glucocorticoid. The patients included in the study were those who had 2 h postlunch and/or 2 h postdinner plasma glucose  $\geq 200$  mg/dl. The detailed inclusion and exclusion criteria are given in Table 1.

## Study procedure

Patients were recruited in the study once they signed the consent form. On recruitment, the patients were randomized to either the control group or the experimental group using computer-generated random numbers. Baseline demographic and clinical data were collected from the hospital records for all patients included in the study.

All oral antidiabetics, premixed insulin, and noninsulin injectable antidiabetics were stopped in both the groups. Patient already taking basal-bolus insulin at home was allowed to continue the same with necessary adjustments as per the group allotted to them.

All patients received fixed carbohydrate meals three times a day. Unless there was a specific reason, all patients received their meals at fixed times of the day.

In all cases, capillary blood glucose (CBG) monitoring was carried out four times a day (three times before meals and at bedtime) using a glucometer. Our hospital uses glucometers

**Table 1: Inclusion and exclusion criteria for the study**

### Inclusion criteria

Nonpregnant patients of ages 18 years and above, with or without diabetes mellitus, admitted to the non-ICU of our hospital from August 2014 to April 2016 who were given glucocorticoid (oral or parenterally) for any indication (minimum dose equivalent to Prednisolone 10 mg) in the past 24 h and had 2 h postlunch and/or 2 h postdinner plasma glucose  $\geq 200$  mg/dl

### Exclusion criteria

Attending physician refusing to allow the patient to be included in the study  
Patients who were discharged from the hospital within 48 h  
Patients who refused to give consent for inclusion in the study  
Patient unable to give consent for inclusion in the study  
Patients who failed to understand either English or Hindi  
Patients refusing to stop their oral antidiabetics, premixed, or basal-plus insulin regimen  
Patients refusing to take insulin  
Patients requiring dialysis  
Patients transferred to the ICU  
Patients requiring enteral or total parenteral nutrition  
Patients requiring intravenous insulin infusion  
Patients on an insulin pump  
Patients with psychiatric issues  
Patients having diabetic ketoacidosis  
Patients receiving oral or parenteral administration of glucocorticoids other than prednisolone, methylprednisolone, dexamethasone, and hydrocortisone  
Patients who have received intra-articular glucocorticoid in the last 48 h  
Patients receiving a single dose of glucocorticoid  
Total duration of glucocorticoid administration was for  $<48$  h  
Glucocorticoid not given daily

ICU: Intensive Care Unit

from the same manufacturer in all the wards and it is regularly calibrated. All glucometer readings were informed to a member of the endocrinology team in real-time and also noted on the nursing charts. Data were obtained from these nursing charts by study investigators the next day.

Adjustments were made to insulin regimen depending on the protocol assigned to the patient. Additional CBG readings were taken if the patient complained of symptoms suggestive of hypoglycemia and/or the treating endocrinologist ordered additional readings. If the additional blood glucose reading was suggestive of hypoglycemia (blood glucose  $<70$  mg/dl) or severe hyperglycemia (blood glucose  $>300$  mg/dl), the readings were counted in the event rate of hypoglycemia or severe hyperglycemia, respectively; however, the readings were not taken to calculate the other glycemic parameters.

Any cases of hypoglycemia (blood glucose  $<70$  mg/dl) were managed according to the existing protocol developed by the endocrinology department. If patient was given any correction for hypoglycemia, then the blood glucose readings for the rest of the day were discarded from the study.

If the patient developed any episode of blood glucose  $>250$  mg/dl, urinary ketones were checked. If any patient developed diabetic ketoacidosis (defined as blood glucose  $>250$  mg/dl, urine

ketone positive, pH <7.3, and serum bicarbonate <18 mEq/L), it was appropriately managed and that patient was excluded from the study. However, if the patient did not have diabetic ketoacidosis, the hyperglycemic excursion was managed as per the protocol assigned to the patient.

If the patient developed blood glucose >400 mg/dl without ketoacidosis, the patient was given additional corrective dose of insulin as per the hospital protocol, irrespective of the group he was randomized to, and blood glucose readings for the rest of the day were discarded from the study. The event was however counted in the even rate for severe hyperglycemia.

### Control group

Treatment protocol for the control group was standard basal-bolus insulin regimen as detailed in the Endocrine Society guidelines.<sup>[5]</sup>

### Experimental group

Patients randomized to the experimental group were managed according to the new protocol developed by us. The basis of this protocol is that giving an additional “correctional insulin” which matches the glycemic profile of the glucocorticoid administered would negate the glycemic effect of the glucocorticoid.

The first step in the experimental group was to classify the patient according to whether they had established diabetes mellitus or developed hyperglycemia secondary to administration of glucocorticoids. They were divided into two groups, namely Group 1 and Group 2.

Group 1 was the group of patients having established diabetes mellitus. Patients included in this group were those who fulfilled any of the following criteria: (a) patient having a history of diabetes mellitus as per their medical records, (b) patients on oral/injectable antidiabetic medications or insulin, and (c) glycated hemoglobin (HbA1c)  $\geq 6.5\%$ .

The second group patients (Group 2) were those who did not have established diabetes mellitus but developed hyperglycemia after administration of glucocorticoids. Patient who did not fulfill any of the criteria enlist above were categorized as Group 2.

The heart of our study was the administration of a “correctional insulin” to be given along with the glucocorticoid depending on the dose and type of glucocorticoid administered. The insulin given as correctional insulin would match the glycemic profile of the glucocorticoid administered. This is presented in Tables 2 and 3.

Apart from the correctional dose of insulin, patients with established diabetes mellitus (Group 1) were given additional background basal-bolus insulin while those in Group 2 were not given any additional background insulin. The indication for background insulin is detailed in Table 4.

Those patients who were assigned to receive additional background insulin (Group 1) were given basal-bolus insulin. The total starting dose of insulin was same as that in the control

**Table 2: Type of correctional insulin to be used along with the glucocorticoid administered in the experimental group**

Glucocorticoid	Type of correctional insulin to be used along with the glucocorticoid
Hydrocortisone	Regular human insulin
Prednisolone	Insulin NPH
Methylprednisolone	Insulin NPH
Dexamethasone	Insulin glargine

NPH: Neutral protamine Hagedorn

group [Table 5]. The total starting dose was divided as 50% basal and 50% bolus insulin. Basal insulin used was insulin glargine, and short-acting bolus insulin used was insulin lispro. The basal insulin glargine was given at bedtime and the dose titrated as shown in Table 6.

Bolus insulin was administered 15 min before each meal. A supplemental dose of short-acting insulin lispro was given depending on premeal CBG readings. The premeal blood glucose readings were informed to the treating endocrinologist on the phone and the supplemental dose of insulin as administered as per the scale shown in Table 7a. This scale is based on the “usual” column of the supplemental insulin scale described in the Endocrine Society guidelines.<sup>[5]</sup> The patients in the control group were given “higher” dose of supplemental correctional insulin based on the “insulin-resistant” column of the supplemental insulin scale described in the Endocrine Society guidelines [Table 7b]. This was an additional dose over and above the scheduled bolus dose of insulin in both control and experimental groups.

Those who were basal-bolus insulin before admission were allowed to continue the same in the experimental group. The basal insulin and bolus insulin were changed to glargine and lispro, respectively, for the purpose of the study. In addition, “correctional insulin” was administered depending on the dose and type of glucocorticoid administered.

Patients were followed up for the entire length of hospital stay till discharge. The discharge advice for the diabetes management was determined by the treating endocrinologist in consultation with the treating physician.

### Measurement of the glycemic parameters

CBG monitoring was carried out four times a day (fasting, prelunch, predinner, and bedtime) using a glucometer.

Data from day 1 of randomization were not used to calculate any of the parameters mentioned below because the patient would be still in a titration phase on day 1. Hence, the blood glucose readings taken to calculate the mean blood glucose and all the other parameters excluded the readings from day 1 in both the control and the experimental groups.

### Comparison of other parameters of glycemic efficacy

Apart from the mean blood glucose, the mean fasting blood glucose, mean prelunch, mean predinner, mean bedtime, and

**Table 3: Dose of the correctional insulin given along with the respective glucocorticoids in the experimental group**

Hydrocortisone dose (mg)	Prednisolone dose (mg)	Methylprednisolone dose (mg)	Dexamethasone (mg)	Insulin dose (units/kg*)
50	10	8	2	0.1
100	20	16	4	0.2
150	30	24	6	0.3
200	>40	32	8	0.4

\*Dose is in units/kg of the body weight of the patient. The type of insulin to be administered is shown in Table 2

**Table 4: Summary of protocol used in the experimental group**

	HbA1c		
	<6.5%	6.5%-8.5%	>8.5%
No diabetes	Correctional insulin along with the glucocorticoid	NA	NA
Undiagnosed diabetes	NA	Background insulin with total starting dose of 0.4 u/kg + correctional insulin administered along with glucocorticoid	Background insulin with total starting dose of 0.5 u/kg + correctional insulin administered along with glucocorticoid
Known diabetic not on basal-bolus insulin	Stop all previous diabetic medications Background insulin with total starting dose of 0.3 u/kg + correctional insulin administered along with glucocorticoid	Stop all previous diabetic medications Background insulin with total starting dose of 0.4 u/kg + correctional insulin administered along with glucocorticoid	Stop all previous diabetic medications Background insulin with total starting dose of 0.5 u/kg + correctional insulin administered along with glucocorticoid
Known diabetic on basal-bolus insulin	Continue the basal-bolus insulin which patient is taking + correctional insulin administered along with glucocorticoid	Continue the basal-bolus insulin which patient is taking + correctional insulin administered along with glucocorticoid	Continue the basal-bolus insulin which patient is taking + correctional insulin administered along with glucocorticoid

Patients aged >70 years in Group 1 received starting dose of background insulin as 0.3 units/kg irrespective of the baseline HbA1c. NA: Not applicable, HbA1c: Glycated hemoglobin

**Table 5: Total starting dose of insulin for patients in the experimental and control group**

HbA1c (%)	Total starting dose of insulin (units/kg)
<6.5	0.3
6.5%-8.5%	0.4
>8.5%	0.5
Age >70 years (irrespective of the HbA1c)	0.3

HbA1c: Glycated hemoglobin

**Table 6: Adjustment of basal insulin dose in the experimental and control groups**

Fasting blood glucose (capillary)	Dose change of basal insulin
>200 mg/dl	Increase basal insulin dose by 20%
140-199 mg/dl	Increase basal insulin dose by 10%
70-100 mg/dl	Reduce basal insulin dose by 10%
<70 mg/dl	Reduce basal insulin dose by 20%

mean premeal blood glucose were calculated from the blood glucose data.

The percentages of blood glucose readings in the target range were calculated. The target range for fasting, prelunch, predinner, and bedtime blood glucose values was determined as 100–140 mg/dl. The target range for bedtime blood glucose was 140–180 mg/dl.

#### Comparison of other parameters of glycemic variability

We compared the parameters for glycemic variability between the two groups. Standard deviation (SD) of blood glucose was

calculated using standard mathematical equation. Mean daily SD is the mean of the SD of blood glucose of each individual day. Mean daily delta blood glucose is the mean of the daily maximum minus daily minimum blood glucose.<sup>[6]</sup> Mean amplitude of glycemic excursion (MAGE) is the mean of the absolute values of the increases or decreases of blood glucose from the nadir or the peak (the increase or decrease should be more than one SD of that day to qualify). Service *et al.*<sup>[7]</sup> have described in detail the procedure for calculating MAGE from CBG readings.

#### Comparison of parameters of safety

Percentage of readings showing hypoglycemia and severe hyperglycemia were calculated for assessment of the safety of the two protocols. Hypoglycemia was defined as blood glucose value <70 mg/dl, and severe hyperglycemia was defined as blood glucose value of >300 mg/dl.

#### Laboratory methods

Plasma glucose concentration was measured with glucose oxidase method on Beckman Coulter Unicel DXC-800 analyzer. HbA1c was measured using ion-exchange high-performance liquid chromatography (Bio-Rad D-10 analyzer). The reference range of the test was from 3.8% to 18.5%.

Contour® Next glucometer was used for CBG measurements (manufactured by Bayer HealthCare LLC). Fingertips were used for CBG sample using standard lancing device provided by the manufacturer. The test strips used flavin adenine dinucleotide-glucose dehydrogenase method for blood glucose testing.<sup>[8]</sup> The results of the glucometer are referenced to plasma/serum blood glucose values. The measuring range of the glucometer is 10–600 mg/dl.



## Statistical analysis

All parametric variables were expressed as mean  $\pm$  SD, and nonparametric variables were expressed as median  $\pm$  interquartile range. Unpaired *t*-test was used to compare the means of parametric data and Mann–Whitney U-test was used to compare nonparametric data. Categorical variables were compared using Chi-square test.  $P < 0.05$  was considered statistically significant. IBM SPSS Statistics version 20.0 software (IBM Co., Armonk, NY, USA) was used for carrying out statistical analysis.

## RESULTS

### Participant flow and patient number

A total of 3110 adult, nonpregnant patients admitted to the nonintensive care unit of our hospital from August 2014 to April 2016 were screened for eligibility. Of these, 234 patients received glucocorticoids for any indication with dose equivalent to prednisolone 10 mg or above. Plasma glucose was checked 2 h after lunch and 2 h after dinner within 24–48 h of the patient receiving the glucocorticoid. A total of 103 patients developed 2 h postlunch and/or 2 h postdinner plasma glucose  $\geq 200$  mg/dl. Five of these patients either declined or were unable to give consent. A total of six patients were excluded because they met one or more of the exclusion criteria. Two of these refused to take insulin and

four of the patients were given enteral or total parenteral nutrition.

The remaining 92 patients were randomized to either experimental or control group. All patients received the allocated intervention. On follow-up during the hospital stay, 10 patients in the experimental group and 11 patients in the control group were excluded. The reasons for exclusions are detailed in Figure 1.

As per our study procedure, CBG readings from day 1 of randomization were excluded in the final analysis. For those patients who developed hypoglycemia which was corrected or severe hyperglycemia which was corrected, the CBG data for the rest of the day were excluded from the analysis. If after exclusion of these CBG readings, the remaining number of CBG was  $\leq 8$ , the patient was excluded from analysis. There were three such patients in the experimental group and one such patient in the control group who was excluded from the final analysis. After all the exclusions, data of 34 patients in the control group and 33 patients in the experimental group were analyzed.

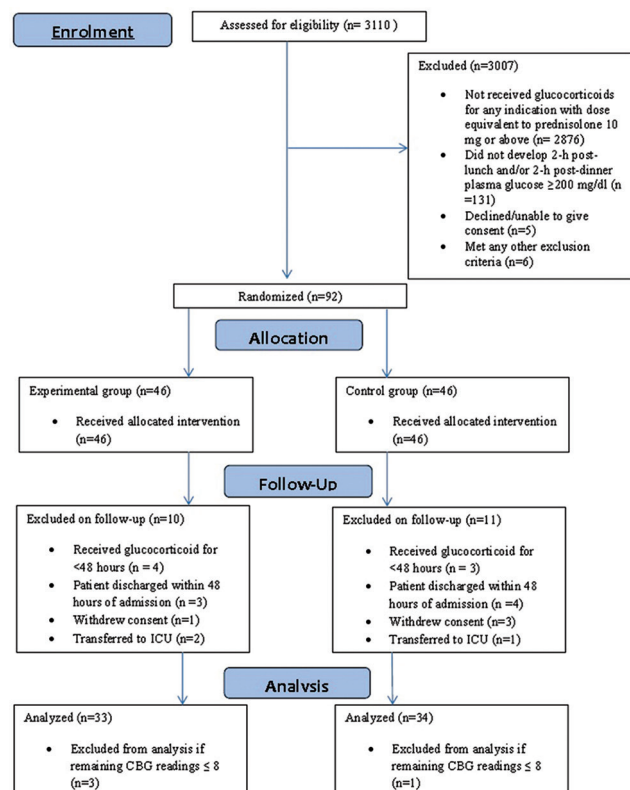
The mean age of the patients in the study was 54 years. 71% of the study patients recruited were males. The mean weight and body mass index of the patients were 71 kg and 25.6 kg/m<sup>2</sup>, respectively. The mean HbA1c was 6.8% and mean creatinine was 1.2 mg/dl. There was no statistically significant difference in the baseline demographic data of the two groups [Table 8].

**Table 7a: Supplemental dose of premeal insulin for experimental protocol**

Blood glucose (mg/dl)	Supplemental insulin dose (units)
>141-180	4
181-220	6
221-260	8 (for premeal capillary blood glucose reading $>250$ mg/dl check for diabetic ketoacidosis as described in the text)
261-300	10
301-350	12
351-400	14
>400	Inform the treating endocrinologist and the study investigators

**Table 7b: Supplemental dose of premeal insulin in the control group**

Premeal capillary blood glucose (mg/dl)	Supplemental short-acting insulin dose (units)
>141-180	6
181-220	8
221-260	10 (for premeal capillary blood glucose reading $>250$ mg/dl check for diabetic ketoacidosis as described in the text)
261-300	12
301-350	14
351-400	16
>400	Inform the treating endocrinologist and the study investigators



**Figure 1: Participant flow diagram (based on consort 2010 flow diagram)**

Patients with established diabetes mellitus who received glucocorticoids as well as nondiabetics who developed hyperglycemia after administration of glucocorticoids were included in the study. Forty-two percent of patients in the experimental group and 64% patients in the control group had preexisting diabetes mellitus. Although the proportion of patients with preexisting diabetes in the experimental and control group was different, the difference was not statistically significant ( $P = 0.08$ ).

Oral prednisolone was the most frequently used glucocorticoid in both the groups. Besides this, oral or parenteral hydrocortisone, methylprednisolone, and dexamethasone were also used. The difference in the proportions of various glucocorticoids used in the two groups was different. However, the proportion of patients receiving prednisolone versus glucocorticoid other than prednisolone was not statistically significant between the two groups ( $P = 0.22$ ).

There was no significant difference among the doses of the prednisolone between the two groups. The dose of all glucocorticoids was converted to the equivalent dose of prednisolone and compared between the two groups. The dose all glucocorticoid when converted to the equivalent dose of prednisolone showed no significant difference between the two groups [Table 9]. Oral prednisolone, when it was used, was most frequently prescribed in the morning time (between 8 and 9 a.m.) in both groups.

### Comparison of parameters of glycemic efficacy between experimental and control groups

The glycemic parameters were compared between experimental and control groups. The mean blood glucose and all the other blood glucose readings including fasting, prelunch, predinner, bedtime, and premeal overall were all significantly lower in experimental group [Table 10 and Figure 2]. The mean blood glucose in the experimental group was 170.32 mg/dl while that in the control group was 214.99 mg/dl. The experimental group had better glycemic control as compared to the control group.

The parameters which assessed the blood glucose in target ranges were higher in the experimental group. However, except for the percentage of premeal blood glucose in target range, the differences were not statistically significant.

The parameters for glycemic variability (SD of blood glucose, SD of premeal blood glucose, mean delta blood glucose, mean daily SD, and MAGE) were all significantly lower in patients in the experimental group [Table 11]. The experimental group had lower glycemic variability as compared to the control group.

The hypoglycemia event rates (hypoglycemia defined by blood glucose <70 mg/dl) were low in both the groups [Table 12]. None of the patients in our study in either of the groups developed severe hypoglycemia (defined as blood glucose <50 mg/dl and/or associated with coma or seizure). No mortality was reported in either of the two groups during the study period.

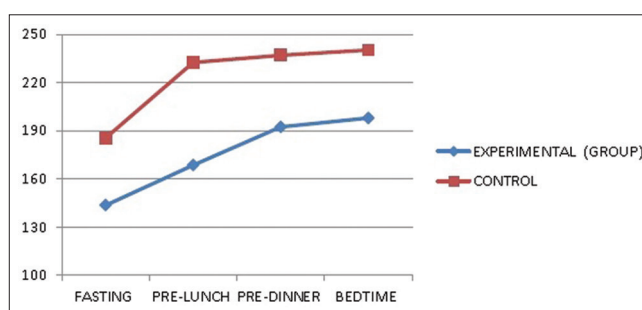
**Table 8: Baseline demographic and clinical characteristics of the two groups**

	Experimental group (n=33)	Control group (n=34)	P
Age (years)	52.97±13.71	55.47±9.92	0.40
Sex (%)			
Male	24 (72)	24 (70)	0.89
Female	9 (28)	10 (30)	
Weight (kg)	71.66±15.55	72.65±17.83	0.82
Body mass index (kg/m <sup>2</sup> )	24.6±6.83	26.77±7.94	0.92
Serum creatinine (mg/dl)	1.02±0.5	1.39±0.73	0.07
HbA1c	6.59±1.57	7.17±1.68	0.16

HbA1c: Glycated hemoglobin

**Table 9: Mean dose of glucocorticoid used in the two groups**

	Experimental group	Control group	P
Prednisolone (mg)	20.37±10.36	20.24±13.93	0.97
All glucocorticoids when converted to equivalent dose of prednisolone (mg)	20.45±10.8	21.06±14.48	0.84



**Figure 2:** Difference in mean blood glucose readings at various time points in the experimental and the control groups (y axis shows blood glucose in mg/dl)

The event rate for severe hyperglycemia (defined as blood glucose >300 mg/dl) was significantly lower in the experimental group [Table 12]. No patients in either of the two groups developed diabetic ketoacidosis during the study.

## DISCUSSION

There are a number of mechanisms by which glucocorticoids cause an increase of blood glucose. Glucocorticoids enhance the hepatic gluconeogenesis, and they cause an increase in the peripheral insulin resistance. They also cause degradation of proteins and lipids providing the substrate for gluconeogenesis.<sup>[9,10]</sup> The inhibition of peripheral glucose uptake by skeletal muscles is seen early after administration of glucocorticoids. This explains the reason that glucocorticoids cause initial postprandial hyperglycemia.<sup>[11]</sup>

Existing literature on the topic of management of GCIH focuses on two major ideas. Studies on the glycemic effects of

**Table 10: Comparison of glycemic parameters in experimental group versus control group**

	Experimental group (n=33)	Control group (n=34)	P
Mean fasting blood glucose (mg/dl)	143.65±37.26	185.48±52.19	0.0001
Mean prelunch blood glucose (mg/dl)	168.52±41.85	232.48±74.6	0.0001
Mean predinner blood glucose (mg/dl)	192.32±53.68	236.88±60.76	0.0001
Mean bedtime blood glucose (mg/dl)	197.86±45.26	240.18±62.19	0.0001
Mean premeal blood glucose (mg/dl)	168.05±37.89	214.99±47.97	0.0001
Mean blood glucose (mg/dl)	170.32±33.46	221.05±49.72	0.0001
Percentage fasting glucose in target range* (IQR)	33.3 (25.0-80.0)	29.2 (00.0-54.7)	0.06
Percentage prelunch glucose in target range* (IQR)	33.3 (00.0-50.0)	00.0 (00.0-28.8)	0.7
Percentage predinner blood glucose in target range* (IQR)	12.5 (00.0-33.3)	00.0 (00.0-17.5)	0.11
Percentage premeal blood glucose in target range* (IQR)	33.3 (15.4-56.3)	15.0 (02.3-28.2)	0.002
Percentage bedtime blood glucose in target range <sup>§</sup> (IQR)	29.3 (00.0-100.0)	16.7 (00.0-40.0)	0.09

\*Target range of premeal blood glucose=100-140 mg/dl; <sup>§</sup>Target range for bedtime blood glucose=140-180 mg/dl. IQR: Interquartile range

**Table 11: Comparison of glycemic variability parameters in experimental group versus control group**

	Experimental group (n=33)	Control group (n=34)	P
SD premeal blood glucose readings (mg/dl)	50.79±18.81	70.5±19.33	0.0001
SD of all blood glucose readings (mg/dl)	51.19±17.67	69.83±18.25	0.0001
Mean daily SD of blood glucose (mg/dl)	39.28±16.31	54.1±18.49	0.0001
Mean daily delta blood glucose (mg/dl)	99.83±39.67	135.66±49.76	0.0001
MAGE (mg/dl)	69.91±27.21	100.52±36.18	0.0001

MAGE: Mean amplitude of glycemic excursion, SD: Standard deviation

**Table 12: Comparison of parameters of safety between experimental and control groups**

	Experimental group (n=33)	Control group (n=34)	P
Hypoglycemia events* (IQR)	00.0 (00.0-00.0)	00.0 (00.0-00.0)	0.3
Severe hyperglycemia events** (IQR)	00.0 (00.0-00.0)	20.7 (06.5-37.7)	0.0001

\*Hypoglycemia event defined as blood glucose <70 mg/dl;

\*\*Hyperglycemia event defined as blood glucose >300 mg/dl.

IQR: Interquartile range

glucocorticoids show that in the initial period, glucocorticoids have a predominant effect on postprandial blood glucose.<sup>[12]</sup> The first school of thought, to tackle GCIH, is increasing the premeal bolus insulin to counteract the postprandial surge of blood glucose. This is also the basis of the current guidelines proposed by the Endocrine Society.<sup>[5]</sup> The use of this basal-bolus insulin approach for GCIH is well established, and there is evidence that it is superior to sliding-scale insulin which was used in the past.<sup>[13]</sup>

An alternative approach was first proposed by Clore and Thurby-Hay.<sup>[14]</sup> In a review article by Perez *et al.*,<sup>[15]</sup> a modified version of the above approach has been proposed for the management of GCIH. The basis of the second school of

thought is that if we can give a specific insulin simultaneously with the glucocorticoid administration, we would be able to negate the hyperglycemic effect of the glucocorticoid.<sup>[15]</sup> The authors have proposed that the type of insulin we would use for neutralizing the glucocorticoid should have the same peaks and duration of action as the hyperglycemic effect of the glucocorticoid.<sup>[14]</sup> A similar approach is followed by the Australian Diabetes Society guidelines for the management of hyperglycemia in indoor patients.<sup>[16]</sup> However, the evidence for the second approach is limited.

Clore and Thurby-Hay<sup>[14]</sup> first recommended an alternative approach to the management of GCIH. They acknowledged the fact the glucocorticoids primarily increased postprandial blood glucose. However, they differed in the explanation to this phenomenon. It is often believed that the postprandial hyperglycemia seen in GCIH is due to the effect of morning glucocorticoids on the peripheral insulin sensitivity. However, Clore and Thurby-Hay<sup>[14]</sup> proposed that the reason for the phenomenon was probably the effect of morning glucocorticoid in causing insulin resistance throughout the day, rather than specific a postprandial defect. They gave an analogy of managing diabetes in pregnancy to explain their theory. Pregnant diabetics initially develop postprandial surge just as it is seen with glucocorticoids. However, as the pregnancy advances and the insulin resistance increases, the requirement of basal insulin progressively increases; however, the bolus ratio for meals (insulin: carb ratio) does not change.<sup>[17]</sup>

The study done by Burt *et al.*<sup>[12]</sup> later in 2011 provides evidence for their theory. The nondiabetic cohort in the study by Burt *et al.*, who received glucocorticoids, developed a hyperglycemic peak after 6–8 h despite not having a significant postprandial glycemic surge. Their major recommendation which helped us shape our protocol was the use of insulin neutral protamine Hagedorn (NPH) along with prednisolone. They also recommended that the dose of the insulin NPH should be based on the dose of the prednisolone administered and weight of the patient.

A number of guidelines recommend the use of NPH along with morning prednisolone. The guidelines by Australian Diabetes

Society<sup>[16]</sup> and a recent guideline by the Joint British Diabetes societies<sup>[18]</sup> endorse similar protocols. Expert reviews on the topic also support the theory.<sup>[14,15,19,20]</sup> The Endocrine Society, however, does not endorse this protocol because of lack of evidence.<sup>[5]</sup>

As far as the glycemic profile of methylprednisolone is concerned, there is little reason to believe that it is any different from that of prednisolone. Seggelke *et al.*<sup>[4]</sup> demonstrated the glycemic profile of morning dose of methylprednisolone in patients with cystic fibrosis. The pattern of glycemia was similar to what we have seen in the studies done for prednisolone.

One of the unique aspects of our protocol is the use of insulin glargine along with insulin dexamethasone and use of regular human insulin along with hydrocortisone. Our recommendation comes from the studies which have shown the glycemic profile of dexamethasone and hydrocortisone as well as its pharmacokinetics.

It is well known that dexamethasone has a longer half-life than other glucocorticoids.<sup>[21]</sup> Sethi *et al.*<sup>[22]</sup> demonstrated that the glycemic effect of dexamethasone starts in about 3 h. Eberhart *et al.*<sup>[23]</sup> and Lukins and Manninen<sup>[24]</sup> showed that glycemic peak due to dexamethasone is at around 9–10 h after administration. The glycemic effect of dexamethasone may last as long as 48 h.<sup>[20]</sup> Insulin glargine has a longer half-life and a longer duration of effect, and hence, it is a more suitable insulin to administer with the dexamethasone. This was the basis of our recommendation.

Hydrocortisone has a much shorter half-life as compared to other glucocorticoids. Vila *et al.*<sup>[25]</sup> showed that hydrocortisone produced a glycemic peak 2 h after administration in healthy volunteers. Since regular human insulin has peak after 2 h, it is perfect insulin to be administered along with hydrocortisone.

There are a few published studies which are similar to our study, which have studied and compared various protocols for the management of GCIH. Grommesh *et al.*<sup>[26]</sup> published a study for the management of GCIH in hospitalized patients. In the study by Grommesh *et al.*, NPH was used irrespective of the type of glucocorticoid used, while in our study we used the “corrective insulin” depending on the type of glucocorticoid which was used.

Ruiz de Adana *et al.*<sup>[27]</sup> published a clinical trial comparing insulin glargine versus insulin NPH as basal insulin in patients with GCIH. The protocol used in the experimental group differs from our study. In our study, we used insulin NPH along with prednisolone over and above the basal-bolus insulin (which included insulin glargine). However, in the study published by Ruiz de Adana *et al.*,<sup>[27]</sup> they have used insulin NPH three times a day before each meal along with the bolus insulin.

Based on the results of our study, we suggest several recommendations for clinical practice. We recommend that all patients who receive glucocorticoids must have multiple

blood glucose measurements for diagnosis of GCIH. We recommend the use of insulin NPH along with prednisolone and methylprednisolone, regular human insulin along with hydrocortisone, and insulin glargine along with dexamethasone as “correctional insulin.” The dose of correctional insulin should be based on the dose of the administered glucocorticoid and weight of the patient. For patients having preexisting diabetes mellitus given glucocorticoids, we recommend using correctional insulin over and above the background basal-bolus insulin regimen. For patients not having preexisting diabetes and developing GCIH, just the correctional insulin dose along with the administered glucocorticoid would suffice.

Our study had several limitations. We proposed using specific insulin as “correctional insulin” for the management of hyperglycemia induced by dexamethasone and hydrocortisone, which was a unique part of our study. However, the number of patients enrolled in the study who received dexamethasone and hydrocortisone was too less to draw any conclusion based on a subgroup analysis. We did not collect data for the dose of insulin used in the experimental and control group. These data would have helped us understand whether there was a difference in insulin requirement between the two groups.

Our study could be a primer for the future research on the field of GCIH. We propose dedicated scientific trials on the management of hyperglycemia secondary to dexamethasone, hydrocortisone, and other glucocorticoids. We also recommend that more studies should be conducted on the dysglycemic effects of systemic as well as other forms of glucocorticoids in both normal volunteers and hospitalized patients to understand the risk factors for GCIH and the glycemic patterns of the administered glucocorticoid.

## CONCLUSION

We developed a new protocol for the management of GCIH among hospitalized patients. The new protocol incorporated the use of “correctional insulin” matching the glycemic profile of the glucocorticoid administered to negate the effect of the glucocorticoid. When compared to the standard basal-bolus insulin protocol, the new protocol showed lower mean blood glucose and lower glycemic variability. The new protocol had lesser episodes of severe hyperglycemia, and the risk of hypoglycemia was negligible.

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## Conflicts of interest

There are no conflicts of interest.

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