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Hyperglycemia Risk Evaluation of Hydrocortisone Intermittent Boluses Vs Continuous Infusion in Diabetic Patients with Septic Shock: A Prospective Cohort Study

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ABSTRACT

Background & Objectives: *Septic shock is a serious condition associated with a high mortality rate because of the multiorgan dysfunction caused by dysregulated host immune responses to infection. Giving low dose steroids in septic shock patients has been shown to hasten the reversal of shock and current Surviving Sepsis Guidelines (SSG) also suggest using low dose steroids for the same. Also, the use of steroids causes hyperglycaemia particularly in diabetic patients. The current SSG does not specify the method of administration. The primary objective of our study was to compare continuous infusion vs intermittent boluses of hydrocortisone to obtain a better glycaemic control.*

Methods: *A prospective cohort study was conducted in diabetic patients with septic shock admitted in Multi-Disciplinary Intensive Care Unit (MDICU) of PRS hospital from July 2022 to February2023. Hydrocortisone was given as continuous infusion in 55 subjects and the remaining 55 received intermittent boluses of hydrocortisone and average blood glucose values were measured in both the groups.*

Results: *Among 110 patients, 55 patients each received continuous infusion and intermittent boluses of hydrocortisone respectively. The mean blood glucose values in continuous infusion group were 161.1 ± 22.7 and 172.5 ± 21.0 (mg/dl) in intermittent boluses group which was statistically significant with a p value of 0.007. There was no statistically significant difference among the groups in 28-day mortality, ICU length of stay (LOS), hospital LOS, or other secondary safety outcomes.*

Conclusions: *This study infers that giving hydrocortisone as continuous infusions in septic shock patients leads to better glycaemic control when compared to intermittent boluses of hydrocortisone, without any difference in 28-day mortality.*

Keywords

Septic shock, Hydrocortisone, Hyperglycemia, Intermittent boluses, Continuous infusion.

Introduction

Septic shock is a serious condition associated with a high mortality rate because of the multiorgan dysfunction caused by dysregulated host immune responses to infection [1,2]. It is a type of vasodilatory shock clinically identified by the requirement of vasopressors to keep mean arterial blood pressure (MAP) greater than 65 mm of Hg and lactate less than 2 mmol/L even after fluid resuscitation [3]. Severe stress conditions may lead to decreased synthesis of serum cortisol and it has been shown that septic shock patients have lower levels of cortisol [4]. Corticosteroids may be useful in this clinical

scenario, as they counteract the uncontrolled inflammatory process that characterizes sepsis and restore cardiovascular homeostasis through salt and water retention [5]. Low dose of hydrocortisone has been showed to be effective in reducing the time until reversal of shock when added to standard therapy in septic shock [6,7].

Surviving sepsis guidelines suggest low-dose hydrocortisone for the treatment of septic shock with ongoing requirement for vasopressor therapy [8]. The recommended dosage of hydrocortisone is 200 mg per day. Guidelines do not specify whether to give hydrocortisone as continuous infusions or intermittent boluses.

The tolerability of low dose hydrocortisone therapy has been good in previous studies and there is no evidence that this low-dose has increased the risk of GI bleeding or risk of secondary infections when used in septic shock. However, hydrocortisone is a potent glucocorticoid and it stimulates gluconeogenesis in both liver and peripheral tissues. It is possible that corticosteroid treatment may induce hyperglycemia and that the need of insulin use may increase with corticosteroid exposure especially in diabetic patients [9]. These effects must also be considered as major adverse events in critically ill patients. Impaired glycemic control has been associated with increased mortality in a heterogeneous population of critically ill patients, and Van den Bergh and co-workers showed that preventing hyperglycemia with insulin substantially improved outcome in critically ill surgical patients [10,11]. This survival benefit was also observed in a recent prospective study in a medical Intensive care unit (ICU) population that required ICU treatment for more than three days [12]. In addition, corticosteroids may increase the risk of critical illness polyneuropathy and myopathy, and therefore the use of corticosteroids may be associated with difficult weaning from mechanical ventilation [9,13]. Prolonged hyperglycemia is one possible pathophysiologic mechanism behind all these complications [14].

The latest surviving sepsis campaign guidelines did not suggest a specific administration method for hydrocortisone due to the lack of enough evidence to prove the association between intermittent hydrocortisone boluses and hyperglycemia [15,16]. The objective of this study was to bridge this gap in the literature by evaluating the risk of hyperglycemia of intermittent boluses vs. continuous infusion of hydrocortisone in critically ill diabetic patients with septic shock. Unlike the previous studies, our study focuses on the effects of low dose hydrocortisone on type II diabetes patients who might benefit from the outcomes of this study.

Methods

This was a prospective cohort study that included type-II diabetic patients who were admitted to MDICU, PRS Hospital fulfills the inclusion and exclusion criteria.

Inclusion Criteria

- Age more than 18 years
- Patients with Type II Diabetes Mellitus
- Patients with septic shock and started on norepinephrine to maintain MAP > 65 mmHg after adequate fluid resuscitation.

Exclusion Criteria

- Patients who exceeded 200mg/day of hydrocortisone,
- Patients who had a contraindication to steroids,
- Patients who died within 24 hours of randomization.
- Patients with a decision of not to resuscitate were excluded.
- Patients deemed unsuitable as per the discretion of the treating physician.

A total of 110 patients who met the inclusion and exclusion criteria were included in the study cohort conducted during the period of July 2022 – February 2023 at PRS hospital, Trivandrum. Institutional ethical committee (IEC) approval was obtained and data were collected after informed and written consents from patients. We looked at many variables including age, gender, SOFA (Sequential Organ Failure Assessment) score, HbA1C levels, Source of infection, need for mechanical ventilation and RRT (Renal Replacement Therapy), Initial RBS (Random Blood Sugar), 28-day mortality, Average blood glucose values, ICU LOS (Length of Stay), hospital LOS, Insulin requirement/day and also secondary safety outcomes like incidence of hypoglycemia, hypokalemia, secondary infections were noted.

All patients were managed according to the Surviving Sepsis Campaign (SSC) guidelines and blood glucose values were included in the analysis (either arterial or venous whole blood sampling or finger-stick capillary testing). Our target was to maintain a blood glucose value of 140-180 mg/dl. When two consecutive blood glucose values exceeded 180 mg/dl, we started the patient on insulin infusion based on Yale insulin infusion protocol and maintained blood glucose values 140-180 mg/dl. Average blood glucose values and insulin requirement / day was noted. Blood glucose values below 75mg/dl was considered as hypoglycemia and were treated according to same protocol.

All the data collected were entered into a Microsoft Excel spread sheet and analyzed using SPSS software version 20.

Categorical and continuous variables were expressed as frequency (percentage)and mean ± SD (Standard Deviation) respectively. Independent ‘t test’ was used to compare continuous variables. Chi-square test was used to find association between categorical variables. A P value of < 0.05 was considered statistically significant.

Results

The baseline characteristics like age, gender was comparable in both the groups and is given in table 1. Compared to other studies available, all the patients enrolled in our study were type II diabetic patients. Hence, we also compared the HbA1C values of both the groups which similar. Majority of the patients in both the groups were admitted with either respiratory infections or urinary tract infections. Number of patients who needed mechanical ventilation and renal replacement therapy in both the groups were also comparable.

Table 1: Baseline characteristics between the two groups.

Patient characteristics		Intermittent boluses (n=55)	Continuous Infusion (n=55)	P value
Age		60.1 ± 9.3	59.4 ± 8.1	0.6
Gender	Male	30 (54.5 %)	34 (61.8 %)	0.4
	Female	25 (45.5 %)	21 (38.2 %)	
SOFA score		7.4	7.6	0.7
Mean HbA1C		7.6	8.0	0.06
Source of infection	Respiratory	20 (36.4 %)	20 (36.4 %)	0.7
	UTI	13 (23.6 %)	17 (30.9 %)	
	SSTI	3 (5.5 %)	1 (1.8 %)	
	Intra-abdominal infection	7 (12.7 %)	9 (16.4 %)	
	Tropical Fever	6 (10.9 %)	3 (5.5 %)	
	Others	6 (10.9 %)	5 (9.1 %)	
Need for RRT	Yes	9 (16.4 %)	7 (12.7 %)	0.6
Need for MV	Yes	7 (12.7 %)	8 (14.5 %)	0.8
Initial RBS		259.9 ± 96.5	240.3 ± 95.3	0.3

SOFA: Sequential Organ Failure Assessment, UTI: Urinary Tract Infection, SSTI: Skin and soft tissue infection, RRT: Renal Replacement Therapy, MV: Mechanical Ventilation, RBS: Random Blood sugar.

The primary and secondary outcomes of this study are given in table 2. The mean blood glucose values in continuous infusion group were 161.1 ± 22.7 and 172.5 ± 21.0 (mg/dl) in intermittent boluses group and this difference in the mean values was statistically significant. Compared to intermittent boluses group, continuous infusion group needed average of 66.3 units/day of human insulin regular while the other group needed only 60.3 units/day, but this difference was not having any statistical significance.

Table 2: Primary and secondary outcomes.

	Intermittent boluses (n=55)	Continuous Infusion (n=55)	P value
Average blood sugar (mg/dl)	172.5 ± 21	161.1 ± 22.7	0.007
28-day mortality	11 (20.0 %)	12 (21.8 %)	0.8
Duration of vasopressor therapy (hours)	42.1 ± 14.2	44.8 ± 9.9	0.3
ICU length of stay (hours)	6.5 ± 1.9	7.3 ± 3.6	0.2
Hospital length of stay (hours)	12.3 ± 3.7	12.5 ± 5.2	0.8
Insulin requirement/day (units/day)	60.2 ± 16.2	66.3 ± 19.1	0.07

Secondary safety outcomes like hypoglycemia were comparable in both the groups (7.3%). Incidence of hypoglycemia was 7.3% in intermittent boluses group and 10.9% in continuous infusion group. Glycemic coefficient of variation in both groups was comparable with no statistically significant difference. The secondary safety outcomes are given in table 3.

Table 3: Secondary Safety Outcomes.

	Intermittent boluses (n=55)	Continuous Infusion (n=55)	P value
Hypoglycemia	4 (7.3%)	6 (10.9%)	0.5
Glycemic coefficient of variation	51.2 ± 3.2	50.3 ± 2.5	0.1
Hypokalemia	4 (7.3%)	4 (7.3%)	1.0

Discussion

Hydrocortisone showed an important role in reversal of shock when added to standard therapy in managing septic shock [6,7,13,15]. But hyperglycemia is one of the most common side effects associated with corticosteroid treatment. From this study we may infer that giving hydrocortisone as continuous infusion leads to better glycemic control compared to intermittent bolus doses.

The primary outcome of our study was the average blood glucose level, and this was 161.1 ± 22.7 mg/dL in continuous infusion group and 172.5 ± 21.0 mg/dL in intermittent boluses group respectively. The difference between blood glucose mean values was 11.4 mg/dL (p=0.007) which was statistically significant. Our study results were comparable with a Randomized Controlled Trial (RCT) by Louisa et al. They found that even though the mean blood glucose levels were similar in the two groups bolus doses of hydrocortisone increased the risk of hyperglycemia compared to continuous infusion. However, in their study the baseline characteristics were not mentioned, also the sample size was only 48 patients in total. Also, they had excluded patients with history of diabetes.

In other recent studies conducted by Ram et Al., Hassan mitwally et al., Tilouche et al. etc, they concluded that there is no statistically significant differences in mean glucose values between the continuous infusion and intermittent boluses group [17-19]. However, these studies were retrospective.

This study reports no difference in 28-day mortality between the two groups. This finding correlates well with previous studies which compared intermittent boluses of hydrocortisone with continuous infusion [17-22]. One of the recent studies – APROCCHSS trial found that all cause ICU and hospital mortality and the 180-day mortality were also significantly lower among corticosteroid treated patients and this observation was different from ours which was expected as our patient profile was different [17].

There was no significant difference between the two groups regarding other secondary efficacy outcomes like hospital length of stay and ICU length of stay. The incidence of hypoglycemia in both the groups were 10.9% and 7.3 % in continuous infusion and intermittent boluses group respectively. There weren't any reported incidences of hypernatremia or steroid induced polyneuropathy or myopathy. Hypokalemia associated with insulin infusion was found to be in 14.5 % of patients in continuous infusion group, whereas only 12.7% patients in intermittent boluses had hypokalemia. The glycemic coefficient of variability was also comparable between both the groups; this observation was in agreement with the study done by Coles et al. [23].

The strength of this study includes relatively larger sample size compared to previous studies and a prospective study design. Also, some of our patients were mechanically ventilated with RT feeds while others were taking feed orally. We didn't consider such factors while determining hyperglycemia risk which might have also contributed to risk of hyperglycemia. The insulin infusion protocol used in the study targeted a blood glucose value of 100-139 mg/dl but we focused on maintaining blood glucose in 140-180 mg/dl range. This might have led to some bias. Also, continuous infusions can be cumbersome and requires attention to intravenous access and drug interactions.

Conclusion

From this study it can be inferred that giving hydrocortisone as continuous infusions in Type-II diabetic patients with septic shock leads to better glycemic control when compared to intermittent boluses of hydrocortisone, without any differences in 28-day mortality.

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