ORIGINAL ARTICLE

Effect of Continuous Infusion vs Bolus Dose of Hydrocortisone in Septic Shock: A Prospective Randomized Study

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Abstract

Aim and background: Corticosteroids are recommended for use in adult patients with septic shock requiring vasopressors for blood pressure maintenance. However, this predisposes them to hyperglycemia, which is associated with a poor outcome. This prospective randomized study compares the effect of continuous infusion with bolus hydrocortisone on blood glucose levels in septic shock.

Materials and methods: Forty adult patients with sepsis and septic shock requiring vasopressor support were randomly allocated to either group C (continuous infusion of hydrocortisone 200 mg/day) or group B (intermittent bolus dose of hydrocortisone 50 mg IV 6 hourly). Blood glucose level (primary objective), number of hyperglycemic and hypoglycemic episodes, daily insulin requirement, shock reversal incidence, time to shock reversal, and nursing workload required to maintain blood glucose within the target range (82–180 mg/dL) were compared.

Results: The mean blood glucose level was comparable in the two groups (136.5 ± 22.08 mg/dL in group C vs 135.85 ± 19.06 mg/dL in group B; $p = 0.921$). The number of hyperglycemic and hypoglycemic episodes ($p = 1.000$ each), insulin requirement/day ($p = 1.000$), and nursing workload ($p = 0.751$) were also comparable among groups. Shock reversal was seen in 7/20 (35%) patients in continuous group and 12/20 (60%) patients in bolus group ($p = 0.113$). Time to shock reversal ($p = 0.917$) and duration of ICU stay ($p = 0.751$) were also statistically comparable.

Conclusion: Both the regimes of hydrocortisone, continuous infusion, and bolus dose, have comparable effects on blood glucose levels in patients with septic shock.

The study was registered prospectively with ctri.nic.in (Ref. No. CTRI/2021/01/030342; registered on 8/1/2021).

Keywords: Blood glucose monitoring, Corticosteroids, Hemodynamic changes, Hydrocortisone, Hyperglycemia, Hypoglycemia, Intensive care units, Randomized controlled trial, Sepsis, Septic shock.

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Highlights

Question: Which of the two regimes of hydrocortisone, continuous infusion or bolus dose, has less impact on the blood glucose levels in septic shock patients?

Findings: Both the regimes of hydrocortisone, continuous infusion, and bolus dose, have similar effects on blood glucose levels in patients with septic shock.

Meaning: Hydrocortisone may be administered either as continuous infusion or as bolus to septic shock without serious blood glucose derangements.

Introduction

Sepsis leads to organ dysfunction as a result of dysregulated response to infection.[1] When sepsis is associated with hypotension unresponsive to fluid resuscitation and raised lactate levels, it is labeled as septic shock. Sepsis and septic shock are one of the leading causes of morbidity and mortality globally accounting for nearly 11 million (19.7%) deaths, even though age-standardized sepsis incidence has fallen by 37% and mortality has decreased by 52.8% from the year 1990 to 2017.[2] Since sepsis is treatable, strengthening the efforts for timely identification and implementation of targeted interventions can improve the outcome.[2,3] One of these interventions is to start insulin when the blood glucose level is ≥180 mg/dL to maintain it in the range of 144–180 mg/dL (8–10 mmol/L).[4]

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Low-dose steroids are advocated as adjunct therapy for septic shock requiring vasopressor therapy.[4] Short-term steroid usage is, however, associated with undesirable effects like deranged blood sugar and neuromuscular weakness. Hyperglycemia can negatively impact the mortality and morbidity of critically ill patients.[5]

A few recent studies have tried to explore different regimes of steroid administration with respect to their effect on blood sugar levels. While intermittent boluses of hydrocortisone is the more commonly administered regime, there are studies where continuous infusion has been used.[6–8] It was demonstrated that hydrocortisone infusion resulted in better control of blood glucose in the range of

72–126 mg/dL when compared to boluses.[6] However, this tight control of blood glucose is no longer acceptable due to frequent hypoglycemic episodes. In contrast to this, higher shock reversal was found with hydrocortisone intermittent boluses compared to infusion.[9] Another trial showed no difference in adverse events or shock reversal in the infusion vs bolus arms of the trial.[10] Thus, the ideal regime of administering low-dose hydrocortisone for the best outcome in septic shock patients is controversial. At the institutional level, uniform rules and protocols must be developed with involvement from multiple specialties, and physicians must become acquainted with them.[11] The present study aims to compare continuous infusion vs intermittent bolus of hydrocortisone in terms of blood glucose control (primary outcome) in critically ill septic shock patients. The secondary outcomes were to compare the two regimes with respect to number of hypoglycemia or hyperglycemia episodes, shock reversal, length of ICU stay, and nursing workload required to maintain blood glucose ≤180 mg/dL.

Materials and Methods

This prospective randomized study was conducted between January 2021 and July 2022 in a tertiary care teaching institute after obtaining approval from the Institutional Ethics Committee-Human Research (vide letter no IECHR/2020/PG/46/83-R1 dated 22/12/2020; 15/12/2020, chairperson: Prof. Siddarth Ramji). The procedures followed were in accordance with the ethical standards set by the committee on human experimentation and with the Helsinki Declaration 1975, as most recently amended. A written and informed consent for participation was taken from the patients or their next of kin before including them in the study. The study was prospectively registered with ctri.nic.in (Ref. No. CTRI/2021/01/030342; registered on 8/1/2021).

Forty patients aged >18 years of either sex were admitted to ICU and diagnosed to have septic shock as defined by the Third International consensus definitions of Sepsis and septic shock[12] and thus requiring norepinephrine to maintain mean arterial blood pressure ≥65 mm Hg were enrolled. Patients with a history of diabetes or those who were on steroid therapy before the current illness were excluded.

Patients fulfilling the inclusion criteria were randomly assigned to one of the two intervention groups using a computer-generated random number table. Group C patients received continuous intravenous infusion of hydrocortisone (200 mg/day diluted in 50 mL normal saline) and group B patients received boluses of hydrocortisone (200 mg/day administered every 6 hours as 50-mg IV diluted to 5 mL). The duration of hydrocortisone treatment was 5 days.

Concealment of randomization was done by means of sequentially numbered sealed opaque envelopes. Blinding of the patient and the nursing staff was ensured by administering four bolus injections of 5 mL normal saline iv every 6 hours in group C and an infusion of 50 mL normal saline over 24 hours in group B. The infusions and boluses were prepared and administered by the nursing staff. The treating physician was not blind to the group allocation.

Blood glucose level was estimated using a glucometer (OK Biotech Co. Ltd., Taiwan) and 0.1 mL of arterial blood. Hyperglycemia was defined as blood sugar >180 mg/dL. Hypoglycemia was defined as <82 mg/dL. Severe hypoglycemia was defined as blood sugar <45 mg/dL. Insulin/glucose infusion was administered using a syringe infusion pump (Smiths Medical Instrument, Zhejiang Co. Ltd., China) as per the NICE-SUGAR study algorithm with a goal to maintain blood glucose levels ≤180 mg/dL.[13] The glucose checks were done every hour. The rest of the management was as per the standard protocol for the management of sepsis and septic shock.[4]

Outcome Measures

The primary outcome was blood glucose control (average blood glucose over the study period). Secondary outcomes included number of hyperglycemic and hypoglycemic episodes, average daily insulin requirement over the period of steroid therapy and number of insulin adjustments/day, shock reversal (stable mean arterial pressure of >65 mm Hg for at least 24 hours without norepinephrine support) and nursing workload (total number of dosage changes in insulin infusion during the study period). The SOFA score, APACHE II score, SAPS II score, sodium levels, lactate levels, and P/F ratio at the time of ICU admission and on all the subsequent days till 5 days of steroid therapy, length of ICU stay, and in-hospital mortality were also noted.

Sample Size Estimation and Statistical Analysis

Loisa et al. observed a standard deviation of 12.6 mg/dL in blood glucose levels in the infusion and bolus group.[6] To estimate a clinically significant difference of 20 mg/dL in mean glucose level at $\alpha = 5\%$ and power = 90%, a sample of 15 cases was required in each group. To account for loss to follow-up and mortality in the ICU, we included 20 cases in each group.

Data was entered in an MS Excel spreadsheet, cleaned, and analyzed using SPSS Version 20.0. Normally distributed continuous variables were expressed as mean ± SD and between-group comparisons were done using an independent Student's *t*-test. Non-normally distributed continuous variables were expressed as median (IQR) and analyzed using the Mann–Whitney *U* test. The within-group comparison was done using repeated measure ANOVA. Categorical variables were expressed as percentages and compared using the Chi-square test /Fisher's exact test. A Kaplan–Meier survival curve was constructed to compare the survival rate between both groups. A *p*-value of < 0.05 was taken as statistically significant.

Results

Fifty-two patients were assessed for eligibility, of whom 40 met the inclusion criteria (Fig. 1). The patient characteristics at the time of enrolment are shown in Table 1. The severity of illness represented by various scores as well as individual parameters was similar between both groups (Table 1).

The blood glucose control was statistically similar between both groups (defined as average of daily blood glucose levels as well as over the 5-day study period) (Table 2). Table 3 depicts the comparison of secondary measures for blood glucose control, all of which were statistically similar between both groups ($p > 0.05$). This includes the number of patients as well as occurrence of hyperglycemia and hypoglycemia over the entire study period.

A comparison of insulin requirements and the number of adjustments needed in its usage showed statistically similar profile between both groups (Table 4). Nursing workload measured as number of total insulin infusion adjustments over the 5-day study period was also statistically similar between both groups (group C: 84 vs group B: 78, $p = 0.751$).

Shock reversal was seen in 7/20 (35%) patients in group C and 12/20 (60%) in group B, $p = 0.113$. The mean time to shock reversal was 84.7 ± 25.3 hours in group C and 83.58 ± 20.58 hours

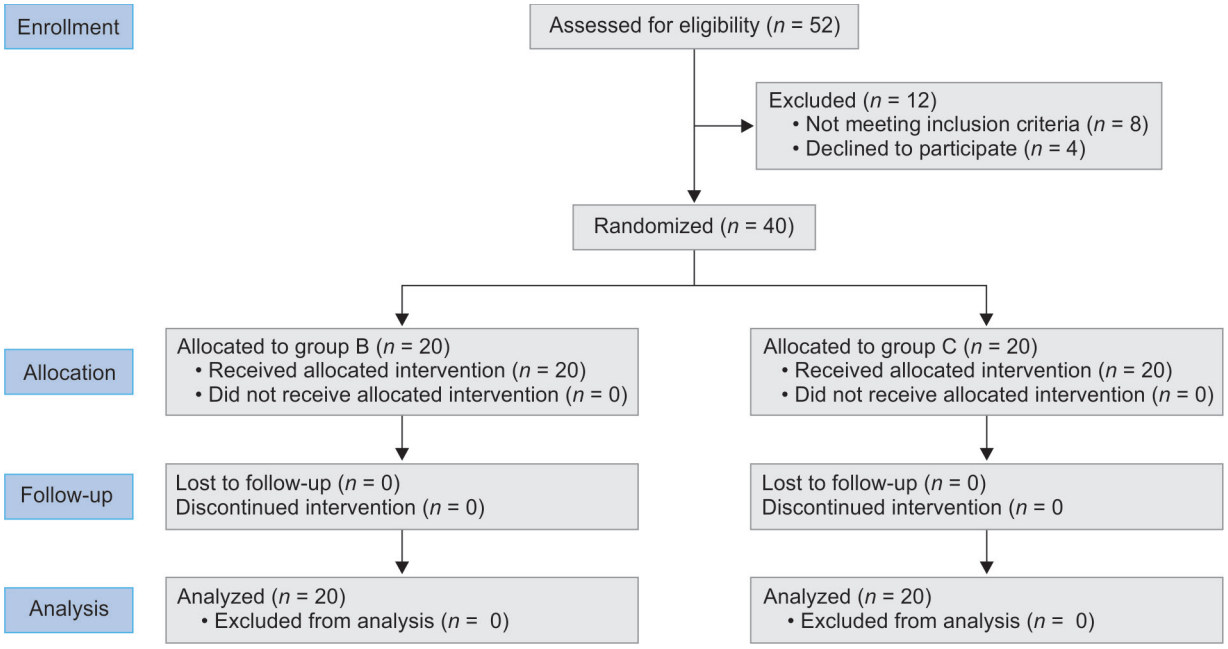

Fig. 1: CONSORT flow diagram

Table 1: Demographic profile and co-morbidities

Parameter	*Group C (n = 20)*	*Group B (n = 20)*	*p-value*
Age (Years)[#]	39 (24.75–63.50)	41.50 (25.25–54.25)	0.957
Sex (Male:Female)	10:10	8:12	0.525
Comorbidities*			
Hypertension	2 (10%)	2 (10%)	1.000
CKD	0 (0%)	0 (0%)	–
CAD	2 (10%)	0 (0%)	0.147
COPD	2 (10%)	2 (10%)	1.000
Asthma	0 (0%)	0 (0%)	–
Malignancy	3 (15%)	2 (10%)	0.633
Need for dialysis*	7 (35%)	12 (60%)	0.113

[#]Values are median (IQR); *values are number(percentage); $p < 0.05$ is significant

Table 2: Blood glucose level

Parameter	*Group C (n = 20)*	*Group B (n = 20)*	*p-value*
Blood glucose control	136.5 ± 22.08	135.85 ± 19.06	0.921
Mean values on daily basis			
Day 1	137.05 ± 26.98	137.15 ± 28.07	0.991
Day 2	136.15 ± 26.39	134.47 ± 25.19	0.842
Day 3	132.06 ± 25.89	137.13 ± 20.91	0.560
Day 4	129.66 ± 17.9	137.0 ± 20.89	0.409
Day 5	135.57 ± 15.47	133.27 ± 15.8	0.766
Lowest value over study period	74.30 ± 23.70	81.10 ± 19.69	0.330

Values are mean ± SD; $p < 0.05$ is significant

in group B, which was comparable ($p = 0.917$). The length of ICU stay was statistically similar between both groups [6 (3.2–10.5) days in group C vs 6 (3.2–15) days in group B; $p = 0.751$], as was the in-hospital mortality [15/20 (75%) in group C and 14/20 (70%) in group B, $p = 0.414$].

Table 3: Hyperglycemic, hypoglycemic and severe hypoglycemic episodes

	Group C (n= 20)	*Group B (n = 20)*	*p-value*
>180 mg/dL*	9 (45%)	10 (50%)	0.752
<82 mg/dL*	9 (45%)	8 (40%)	0.749
<45 mg/dL*	4 (20%)	1 (5%)	0.151
Hyperglycemic episodes[#]	44	41	1.000
Hypoglycemic episodes[#]	16	14	1.000
Severe hypoglycemic episodes[#]	5	1	0.339

*Values are number of patients (percentage); [#]values are number of episodes; $p < 0.05$ is significant

Table 4: Insulin requirement and number of insulin adjustments

Parameter	*Group C (n = 20)*	*Group B (n = 20)*	*p-value*
Insulin requirement (IU/day)			
Day 1	0 (0–3)	0 (0–2)	0.747
Day 2	0 (0–0)	0 (0–1)	0.171
Day 3	0 (0–2)	0 (0–1)	1.000
Day 4	0 (0–1)	0 (0–1.5)	1.000
Day 5	0 (0–2)	0 (0–0)	1.000
Number of insulin infusion adjustment			
Day 1	0 (0–4)	0 (0–2)	0.747
Day 2	0 (0–0)	0 (0–2)	0.171
Day 3	0 (0–2)	0 (0–2)	1.000
Day 4	0 (0–1)	0 (0–1.5)	1.000
Day 5	0 (0–2)	0 (0–0)	1.000

Values are median (IQR); $p < 0.05$ is significant

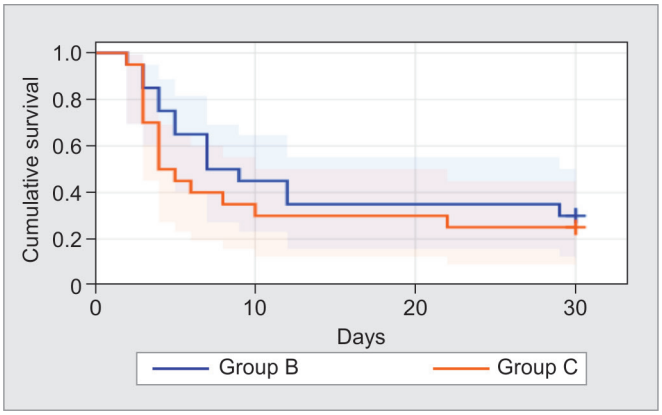

Fig. 2: Kaplan–Meyer survival curve ($p = 0.414$)

A Kaplan Meier analysis showed a median survival time of 4 days (95% CI: 3.10–4.89) for group C vs 5 days (95% CI: 2.80–7.20) for group B and (p-value with log rank = 0.414) (Fig. 2).

Discussion

This study was conducted to compare blood glucose control when low-dose continuous infusion or intermittent bolus of hydrocortisone was given to critically ill patients with septic shock. The major findings of the study were that there was no difference in the blood glucose control with the two regimes of low-dose hydrocortisone. The insulin requirement and the nursing workload also did not differ between the groups. Though the time to shock reversal was statistically similar between groups, a clinically larger, though statistically similar, number of patients in the bolus group had shock reversal. The length of ICU stays and the in-hospital mortality and survival time were also comparable.

Low-dose steroids like hydrocortisone have been recommended for patients with septic shock requiring vasopressor therapy.[4,14] This is advocated as nearly 50% of patients suffering from septic shock have adrenal insufficiency.[15,16] Corticosteroids may help by improving the hemodynamics, decreasing catecholamine requirements, reversal of shock and organ system failure with an ultimate reduction in mortality.[17]

Previous studies have used hydrocortisone in a dose of 200–300 mg.[6,10] When used in a dose of 300 mg/day, no additional benefit could be demonstrated.[10] As per SSC guidelines 2021, initiation of hydrocortisone in a dose of 200 mg/day bolus or 50 mg every 6 hourly may be done after at least 4 hours of norepinephrine at the rate of ≥0.25 µg/kg/min.[4]

Thus, in this study, we used hydrocortisone in the dose recommended by the 2016 guidelines and administered it either as a 200 mg/day continuous infusion or as 50 mg bolus every 6 hours.

The duration of hydrocortisone therapy has also been variable in the previous trials. In the VANISH trial, 50 mg hydrocortisone bolus 6 hourly was administered for 5 days and then tapered to 50 mg 12 hourly for the next 3 days and 50 mg once daily for another 3 days.[18] In ADRENAL[7] and APROCCHSS[19] trials the duration of hydrocortisone therapy was 7 days. In our study, we used it for a period of 5 days.

The Surviving Sepsis Campaign Guidelines strongly recommended a protocolized approach to blood glucose management in ICU patients with sepsis. Since the target blood glucose between 82 and180 mg/dL is associated with better outcome in septic patients in terms of hypo/hyperglycemic episodes, insulin consumption, and ICU mortality, we set a target blood glucose level ≤180 mg/dL for our patients and followed the NICE-SUGAR algorithm[13] to maintain these levels.

Loisa et al. compared the two regimes of steroid administration and targeted blood glucose was 72–126 mg/dL. Similar to our findings, they found that the mean blood glucose levels were comparable with both regimes. However, they reported a significantly higher number of hyperglycemic episodes in the bolus group, 15.7 ± 8.5 vs 10.5 ± 8.6 in the infusion group, $p = 0.039$, and higher nursing workload in bolus group. Multiple hypoglycemic episodes were also reported with no significant difference in shock reversal.[6] Such results observed by Loisa et al. may be because of the tight range of blood sugar control targeted in this study. The tighter blood sugar regulation range also explains the higher nursing workload observed by them with bolus therapy compared to continuous infusion. However, more liberal target blood sugar ranges (82–180 mg/dL) may have resulted in comparable hypo/hyperglycemic episodes, number of insulin adjustments, and nursing workload with the two regimes in our study.

Shock reversal was reported to be higher (66%) with the bolus doses compared to 35% with continuous infusion of hydrocortisone ($p = 0.008$) in a study by Tilouche et al.[9] We also obtained similar shock reversal figures in our study, but significant difference between the two groups was not observed probably because our study was not powered to detect a significant difference in this parameter. Similar to our findings, this study also reported a median time to shock reversal as 5 days in the bolus group compared to 6 days in continuous infusion group (log rank = 0.048). Contrary to this, Ibarra-Estrada et al. found that shock reversal was higher (83 vs 63%, $p = 0.004$) and time to shock reversal was shorter with a continuous infusion of hydrocortisone. Their results showed that the initiation of hydrocortisone was 6 hours later in the bolus group compared to continuous infusion group which probably may be the reason for a poorer outcome in the bolus group.[20] Similar to our results, Hoang et al.[21] found that both regimes were comparable in the resolution of septic shock.

The in-hospital mortality figures reported by Hoang et al.[21] were close to those observed in our study. However, the rate was higher compared to that reported in other studies[9,14] because the disease severity score of the patients enrolled in our study was very high. This is partly because we are a developing country with limited resources and poor hospital beds to ICU ratio. Consequently, only very sick patients with advanced disease can be accommodated in the ICU which accounts for such poor outcome.

Our study has its own strengths. To the best of our knowledge, there is no previous study estimating blood glucose control in the Indian population. Blinding of the observers was ensured by the use of saline infusion pumps in the bolus group and saline boluses in the infusion group as described in the methods section. Glucose estimation was done using arterial sample, which is superior to the capillary blood in patients with shock. However, there are a few limitations as well. We did not standardize the time to initiate hydrocortisone in relation to the vasopressor therapy duration. The caloric intake of the patients was not protocolized during the course of study, which could have had an impact on the blood sugar. We could not measure the cardiac indices as ours is a resource-limited setting. So, the vasopressor therapy was based only on the mean arterial pressure. Also, for the same reason, we were occasionally not able to provide higher culture-specific antibiotics to our patients, which could have contributed to the high mortality. We included patients with no history of

diabetes so the glycemic control among the diabetics with the two modalities cannot be commented upon. Also, we could not exclude unknown diabetes due to the inability to perform HbA1c as a routine test on admission.

Conclusion

From the above findings, we conclude that both continuous infusion and bolus dose of hydrocortisone have similar effect on blood glucose control, insulin requirement, and number of hyper/hypoglycemic episodes. Both regimes are similar with respect to the nursing workload, time to shock reversal, ICU mortality, and duration of ICU stay. However, since the shock reversal rate is clinically higher in the bolus regime compared to continuous infusion regime, further studies to evaluate the same may be planned.

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