International Journal of Pharmacology

ISSN 1811-7775

science alert

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Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2024.832.840

Research Article
An Evaluative Comparison of Continuous Versus Intermittent Hydrocortisone Administration in the Therapeutic Approach to Septic Shock

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Abstract

Background and Objective: The pathophysiology of septic shock is intricately associated with immune dysregulation and inflammatory responses. Hydrocortisone inhibits excessive inflammation, but optimal dosage and administration methods remain debated. This study purports to appraise and juxtapose the therapeutic efficacies of continuous and intermittent hydrocortisone administration regimens in managing septic shock. **Materials and Methods:** A retrospective scrutiny of clinical data was performed involving 73 patients diagnosed with septic shock from March, 2019 to February, 2022. The patients were dichotomized into two groups: The continuous group (administered with an unremitting intravenous infusion of hydrocortisone) and the intermittent group (treated with sporadic slow intravenous drips of hydrocortisone), comprising 40 and 33 cases, respectively. The MBG, LAGE, hyperglycemic time window and GV were significantly diminished in the continuous group vis-à-vis the intermittent group, with the differences bearing statistical significance ($p<0.05$). **Results:** Relative to pre-treatment values, PCT, hs-CRP, IL-1β, IL-6, TNF-α and HMGB-1 concentrations were significantly reduced in both groups at the 96 hrs treatment mark and were lower in the continuous group ($p<0.05$). Relative to pre-treatment values, $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ were significantly elevated in both groups at the 96 hrs treatment mark and were higher in the continuous group, while $CD8^+$ was significantly reduced and was lower in the continuous group ($p<0.05$). **Conclusion:** Compared with intermittent hydrocortisone administration, continuous hydrocortisone treatment demonstrated superior efficacy in managing septic shock. The continuous regimen notably mitigated blood glucose variability, regulated oxygen metabolism, suppressed inflammatory responses and enhanced immune functionality. However, it presented no significant advantages concerning hemodynamic parameters and short-term prognostic indices.

Key words: Septic shock, hydrocortisone, continuous therapy, intermittent therapy, hemodynamics

Citation: Chen, X. and L.H. Ji, 2024. An evaluative comparison of continuous versus intermittent hydrocortisone administration in the therapeutic approach to septic shock. Int. J. Pharmacol., 20: 832-840.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Sepsis represents a prevalent clinical syndrome incited by various triggers such as surgical procedures, traumatic injuries and burns. This condition exhibits a high incidence rate and grave clinical manifestations, leading to considerable morbidity and mortality. Despite the application of hemodynamic support, infection focus clearance and antimicrobial agents, the mortality rate for sepsis patients remains staggeringly high, oscillating between 30-50%[1,2]. Sepsis exhibits a swift progression and, if not promptly and effectively countered, may deteriorate into septic shock. This advanced stage of the disease primarily manifests as acute circulatory failure, exacerbating the patient's condition and complicating the treatment process[3].

Septic shock is classified as a subtype of severe sepsis and is one of the predominant causes of fatality in critical care medicine. Notwithstanding advancements in medical technology, the mortality rate associated with this disease remains high and its incidence shows a proclivity for gradual augmentation[4,5]. As a consequence, the development of efficacious therapeutic strategies for septic shock continues to be an area of fervent clinical research.

The pathophysiology of septic shock is intricately associated with immune dysregulation and inflammatory responses. Glucocorticoids have been demonstrated to efficaciously inhibit excessive inflammatory responses[6] and are thus widely employed in the clinical management of patients with septic shock[7]. Hydrocortisone, a commonly used glucocorticoid, exerts anti-shock, antiviral, anti-inflammatory and immunosuppressive effects. Its anti-inflammatory effect surpasses that of cortisone by 1.25-fold, thereby rendering it more efficacious in treating sepsis and septic shock[8,9].

However, the specifics concerning the method and dosage of hydrocortisone administration in treating septic shock have yet to attain a consensual conclusion in clinical practice. The current therapeutic approach predominantly involves two regimens: Continuous intravenous infusion and intermittent slow intravenous drip. This study, therefore, retrospectively evaluates the clinical data of 73 patients with septic shock, to compare the clinical efficacies of these divergent hydrocortisone administration strategies in managing septic shock. The findings are detailed herein.

MATERIALS AND METHODS

General data

Participant characteristics: This study undertook a retrospective analysis of clinical data from 73 patients with septic shock, treated at our institution from March, 2019 to February, 2022. The cohort comprised 44 males and 29 females, aged between 28-77 years with a mean age of (55.75±6.84) years. The body mass index ranged from 17-34 kg/m^2 with a mean of (22.19±2.06) kg/m^2. The underlying conditions included 18 cases of sepsis, 32 cases of severe pneumonia, 12 cases of acute peritonitis and 11 instances of biliary tract infection. The cohort was stratified into two groups based on the treatment regimen, viz., the continuous group (n = 40) and the intermittent group (n = 33).

Ethical consideration: This study was approved by the Ethics Committee of Xingyuan Hospital of Yulin. The research objects were informed and they signed a fully-informed consent form.

Eligibility criteria

Inclusion criteria: Participants were required to meet the diagnostic guidelines for septic shock as defined by Li *et al.*[10]; possess comprehensive clinical data; be aged between 18 and 80 years; demonstrate signs of tissue hypoperfusion even after standardized fluid resuscitation treatment and require continuous intravenous administration of norepinephrine therapy.

Exclusion criteria: Participants were excluded if they had known allergies to hydrocortisone or any other medications used in this study; were pregnant or lactating; had concurrent malignancies, hematological conditions, immune function abnormalities or autoimmune diseases; had received glucocorticoid therapy within three months prior to enrolment; had suffered paraquat poisoning; had diabetes; were afflicted with severe infectious diseases or psychiatric conditions or had an expected hospitalization duration of less than 24 hrs.

Methodology: All participants received symptomatic interventions including anti-infection measures, fluid resuscitation, intensive insulin therapy, pulmonary protective ventilation and measures to ensure organ tissue perfusion upon admission. Participants in the continuous group were administered hydrocortisone (Tianjin Biochemical Pharmaceutical Co. Ltd., H12020486) via continuous intravenous infusion at a rate of 8.33 mg/hr over a period of 5 days. The intermittent group received hydrocortisone through a single slow intravenous drip, dosed at 20 mg/day over a 2 hrs period, continued for 5 days.

Observation indexes

Clinical efficacy: Efficacy was stratified into three categories. "Substantial Efficacy" was noted when the patient's condition was stable, consciousness normalized, systolic blood pressure exceeded 90 mmHg and urine output exceeded 30 mL/hr. "Partial Efficacy" was recorded when the patient's condition showed improvement, consciousness significantly improved, systolic blood pressure exceeded 90 mmHg, urine output significantly increased and hemodynamic stability was maintained through medication. "Inefficacy" was classified when the aforementioned criteria were not met. The total efficacy rate was the aggregate of the substantial and partial efficacy rates.

Hemodynamic parameters: The Extravascular Lung Water Index (EVLWI), heart rate (HR), Central Venous Pressure (CVP) and mean arterial pressure (MAP) were monitored via a cardiac monitor before treatment and at 6, 24, 48 and 96 hrs post treatment initiation.

Glycemic control: The large amplitude of glycemic excursions (LAGE), mean blood glucose (MBG), glycemic variability (GV) and the hyperglycemic time window were monitored via a continuous glucose monitor. The hyperglycemic time window was defined as the proportion of time in 24 hrs where blood glucose levels exceeded 10.0 mmol/L.

Oxygen metabolism parameters: Oxygenation index (OI) and lactate concentration were assessed and calculated via a cardiac monitor before treatment and at 24 hrs post-treatment initiation.

Inflammatory response: Six milliliters of peripheral venous blood was collected from patients in both groups, centrifuged at 3500 r/min for 10 min and the serum was assayed via ELISA to determine the levels of serum hypersensitive C-Reactive Protein (hs-CRP), Interleukins (IL-1β, IL-6), Tumor Necrosis Factor-α (TNF-α), Procalcitonin (PCT) and High Mobility Group Box Protein-1 (HMGB-1). These measurements were performed before treatment and at 96 hrs post treatment initiation. Assay kits were procured from Nanjing Wanmuchun Biotechnology Co. Ltd. (Product Nos: WM-YX11183, CSB-E08053h, SEKH-0013, E-EL-H0109c, XY1004A, E-EL-H1554c).

Immunological parameters: The T-lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$) were quantified using the Beckman CytoFLEX flow cytometer before treatment and at 96 hrs post treatment initiation.

Prognostic indicators: Comparative analysis was conducted between the two groups with respect to the duration of ICU stay, length of hospitalization, duration of shock and 28 days morbidity and mortality rates.

Statistical analysis: Data analysis was performed using SPSS software (version 23.0). The Shapiro-Wilk test was employed to verify normal distribution of the data. Measurement data (hemodynamic parameters, dynamic blood glucose level, oxygen metabolism level, inflammatory response, immune function, length of ICU stay, length of hospitalization and shock duration) conforming to normal distribution were expressed as ($\bar{\chi}\pm S$) and analyzed using a t-test. Count data (28 days morbidity and mortality rate) were represented as n (%) and analyzed using a χ^2 test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Baseline information: No statistically significant disparities were observed in terms of gender, age, underlying disease, body mass index, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, mean arterial pressure (MAP) and cortisol levels between the continuous and intermittent groups ($p>0.05$) (Table 1).

Clinical efficacy: The total efficacy rate was significantly higher in the continuous group (77.50%) compared to the intermittent group (54.55%) ($p<0.05$) (Table 2).

Hemodynamic parameters: No statistically significant differences were observed between the Extravascular Lung Water Index (EVLWI), Central Venous Pressure (CVP), heart rate (HR) and mean arterial pressure (MAP) in patients in the continuous and intermittent groups before treatment ($p>0.05$). The EVLWI and HR were significantly reduced, while MAP was significantly elevated in both groups at 6, 24, 48 and 96 hrs post-treatment initiation compared to the baseline values ($p<0.05$). Furthermore, CVP was significantly increased in both groups at 24, 48 and 96 hrs ($p<0.05$). However, there were no significant differences between the EVLWI, CVP, HR and MAP at 6, 24, 48 and 96 hrs post-treatment initiation in either group ($p>0.05$) (Table 3).

Table 1: Comparison of baseline information n/($\bar{\chi}\pm$S)

Group	Gender		Age (years)	Body mass index (kg/m^2)	Underlying disease				APACHE II score (points)	MAP (mmHg)	Cortisol (nmol/L)
	Male	Female			Sepsis	Severe pneumonia	Acute peritonitis	Biliary tract infection			
Intermittent group (n = 33)	21	12	56.14±7.33	22.31±2.15	7	15	4	7	21.53±2.05	54.02±5.01	451.08±118.82
Persistent group (n = 40)	23	17	55.69±7.18	22.03±2.31	11	17	8	4	21.29±2.15	53.72±4.78	453.85±125.52

Table 2: Comparison of clinical efficacy between two groups n (%)

Group	Apparent effect	Effective	Ineffective	Total effective
Intermittent group (n = 33)	10 (30.30)	8 (24.24)	15 (45.45)	18 (54.55)
Continuous group (n = 40)	15 (37.50)	16 (40.00)	9 (22.50)	31 (77.50)
χ^2				4.317
p-value				0.038

Table 3: Comparison of hemodynamics at different time points ($\bar{\chi}\pm$S)

Group	Time	EVLWI (pg/mL)	CVP (mmHg)	HR (beats/min)	MAP (mmHg)
Intermittent group (n = 33)	Before treatment	17.25±2.38	7.89±1.68	114.65±12.02	55.25±4.35
	6 hrs-treatment	12.51±1.85*	8.35±1.75	96.85±10.11*	69.02±5.66*
	24 hrs-treatment	11.32±2.02*	11.85±2.06*	94.25±11.02*	69.88±6.02*
	48 hrs-treatment	10.23±1.68*	11.54±2.15*	86.32±8.21*	70.15±5.75*
	96 hrs-treatment	8.32±1.43*	10.72±2.02*	81.02±7.56*	70.22±5.37*
Continuous group (n = 40)	Before treatment	17.38±2.24	7.76±1.82	115.02±13.14	54.85±5.16
	6 hrs-treatment	12.25±1.76*	8.12±1.79	96.21±11.05*	68.58±5.20*
	24 hrs-treatment	11.12±1.93*	11.67±1.98*	94.02±10.55*	68.35±6.02*
	48 hrs-treatment	10.03±1.72*	11.21±2.01*	85.43±8.58*	68.21±5.71*
	96 hrs-Treatment	8.15±1.32*	10.21±1.88*	80.03±8.55*	70.01±5.86*

*p<0.05 compared with pre-treatment

Table 4: Comparison of inflammatory responses between the two groups ($\bar{\chi}\pm$S)

Group	Time	PCT (ng/L)	hs-CRP (mg/L)	IL-1β (μg/L)	IL-6 (μg/L)	TNF-α (ng/L)	HMGB-1 (ng/L)
Intermittent group (n = 33)	Before treatment	5.28±0.85	33.25±3.36	435.18±38.62	235.28±20.21	92.58±8.12	45.35±4.42
	96 hrs-treatment	3.01±0.65*	21.05±3.18*	291.05±23.18*	168.52±15.62*	70.32±6.52*	29.05±2.95*
Continuous group (n=40)	Before treatment	5.19±0.78	32.79±3.28	434.02±36.28	236.52±21.02	93.15±8.44	44.82±4.19
	96 hrs-treatment	1.56±0.56*#	14.26±2.74*#	214.26±20.74*#	121.35±210.58*#	50.24±6.02*#	20.03±2.65*#

*p<0.05 compared to pre-treatment and #p<0.05 compared to intermittent group

Glycemic control: Mean blood glucose (MBG) (Fig. 1a), large amplitude of glycemic excursions (LAGE) (Fig. 1b), hyperglycemic time window (Fig. 1c) and glycemic variability (GV) (Fig. 1d) were significantly lower in the continuous group compared to the intermittent group (p<0.05) as shown in Fig. 1.

Oxygen metabolism parameters: No significant differences were observed in the oxygenation index (OI) and lactate concentration between the continuous and intermittent groups before treatment (p>0.05). The OI was significantly elevated at 24 hrs post-treatment initiation in both groups and was higher in the continuous group (Fig. 2a). Conversely, lactate concentration was significantly reduced and was lower in the continuous group (p<0.05) (Fig. 2b).

Inflammatory response: No significant differences were observed in procalcitonin (PCT), Hypersensitive C-Reactive Protein (hs-CRP), Interleukins (IL-1β, IL-6), Tumor Necrosis Factor-α (TNF-α) and High Mobility Group Box Protein-1 (HMGB-1) between the continuous and intermittent groups before treatment (p>0.05). All these markers showed a significant reduction at 96 hrs post-treatment initiation in both groups, with a more pronounced decrease in the continuous group (p<0.05) (Table 4).

Immune function: No significant differences were observed in T-lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$) between the continuous and intermittent groups before treatment (p>0.05). The $CD3^+$ (Fig. 3a), $CD4^+$ (Fig. 3b) and $CD4^+/CD8^+$ (Fig. 3d) showed a significant increase at 96 hrs post-treatment initiation in both groups, with a more pronounced increase in the continuous group, while $CD8^+$ significantly decreased and was lower in the continuous group (Fig. 3c) (p<0.05).

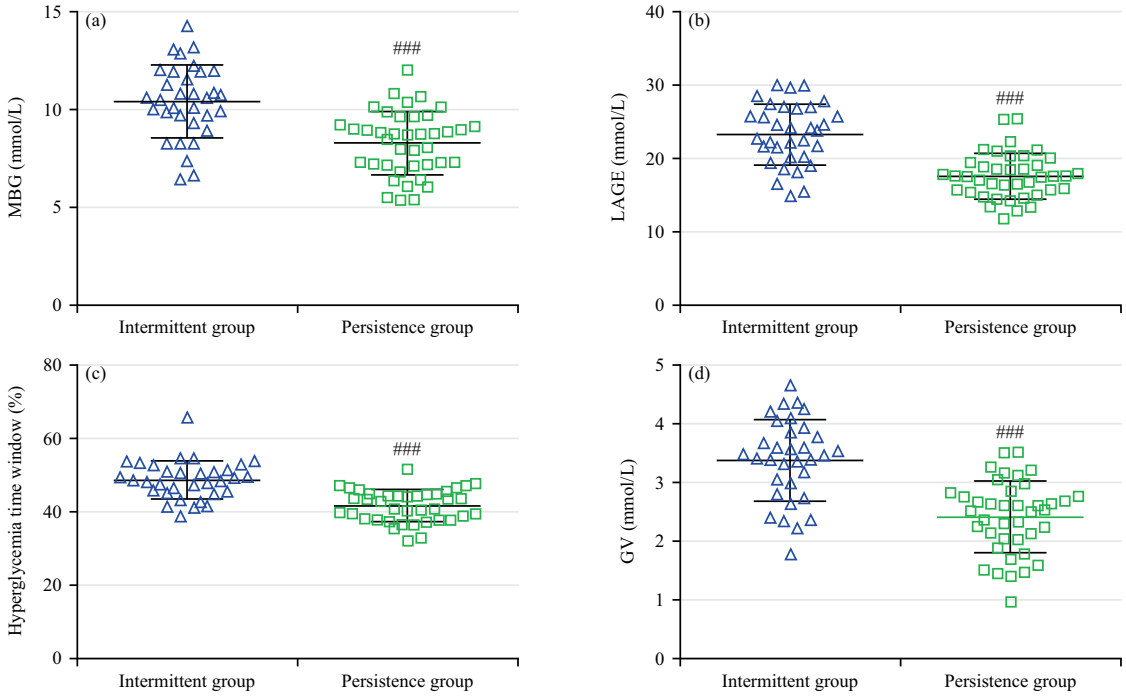

Fig. 1(a-d): Impact of continuous and intermittent hydrocortisone treatment on dynamic blood glucose in septic shock patients. Patients in the continuous hydrocortisone treatment group demonstrated significantly lower levels of (a) MBG, (b) LAGE, (c) Hyperglycemic time window and (d) GV in comparison to the intermittent group

A comparison with the intermittent group revealed a significant difference and ***p<0.001

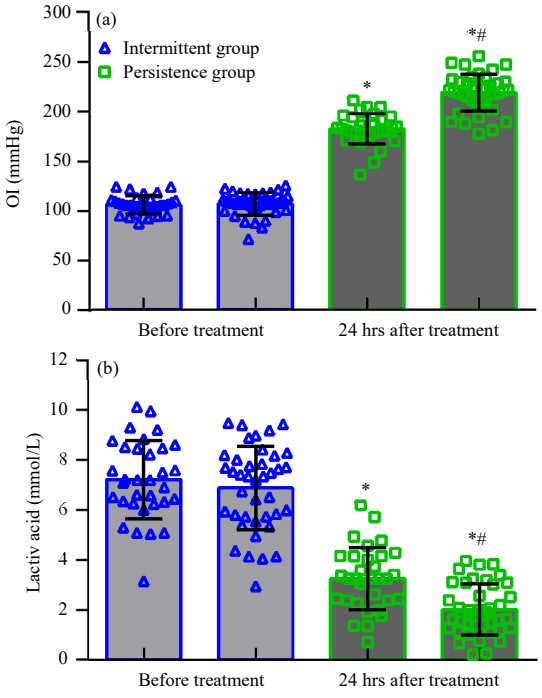

Fig. 2(a-b): Influence of continuous and intermittent hydrocortisone treatment on oxygen metabolism levels in septic shock patients. Patients in the continuous hydrocortisone treatment group had (a) Significantly increased OI and (b) Significantly decreased lactate concentration compared to the intermittent group

*p<0.05 relative to pre-treatment and #p<0.05 relative to the intermittent group

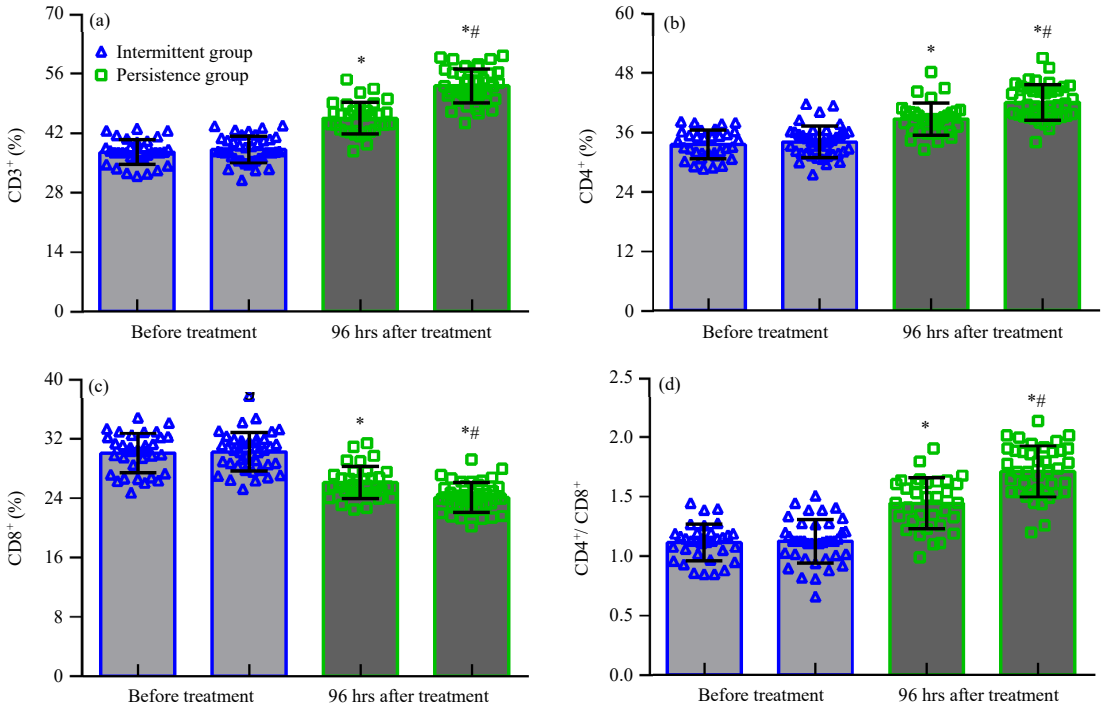

Fig. 3(a-d): Effect of continuous and intermittent hydrocortisone treatment on immune function levels in septic shock patients. Patients in the continuous hydrocortisone treatment group had significantly elevated (a) $CD3^+$, (b) $CD4^+$, (c) $CD8^+$ was significantly lower than in the intermittent group (d) $CD4^+/CD8^+$ levels compared to the intermittent group

*p<0.05 compared with pre-treatment and #p<0.05 compared with the intermittent group

Prognostic indicators: No significant differences were observed in ICU length of stay (Fig. 4a), overall hospital stay (Fig. 4b), shock duration (Fig. 4c) and 28 days morbidity and mortality rates (Fig. 4d) between the continuous and intermittent groups (p>0.05).

DISCUSSION

Sepsis stands as a leading cause of death among critically ill patients, presenting an intimidatingly high mortality rate and engendering formidable healthcare costs[11,12]. This serious medical condition, triggered predominantly by systemic immune dysfunction and enhanced capillary permeability due to infectious factors, results in multi-organ failure due to insufficient perfusion of essential organs[13]. Septic shock is the most severe manifestation of sepsis and its management remains arduous, with glucocorticoids frequently employed to mitigate the disease by significantly reducing the aggregation and release of inflammatory cytokines and curtailing capillary leakage[14,15].

Hydrocortisone, a common clinical glucocorticoid, has been widely recognized for its antiviral, anti-inflammatory, anti-shock and immunosuppressive properties, with its efficacy documented in septic shock and sepsis treatment[16,17]. However, the usage and dosing regimen of hydrocortisone continues to be a matter of controversy. This study found the total efficacy rate in the continuous group surpassed that of the intermittent group; oxygenation index (OI) was notably enhanced in both groups 24 hrs into the treatment, even more so in the continuous group, while lactate concentration was markedly diminished, especially in the continuous group. Notably, variables like Extravascular Lung Water Index (EVLWI), Central Venous Pressure (CVP), heart rate (HR), mean arterial pressure (MAP) as well as Intensive Care Unit (ICU) stay, length of hospital stay, duration of shock and 28 days morbidity and mortality rates showed no significant differences at various intervals between both groups. This suggests that continuous hydrocortisone treatment offers greater efficacy in septic shock management, effectively regulating oxygen metabolism, albeit no significant advantage in hemodynamics and short-term prognosis was discerned[18].

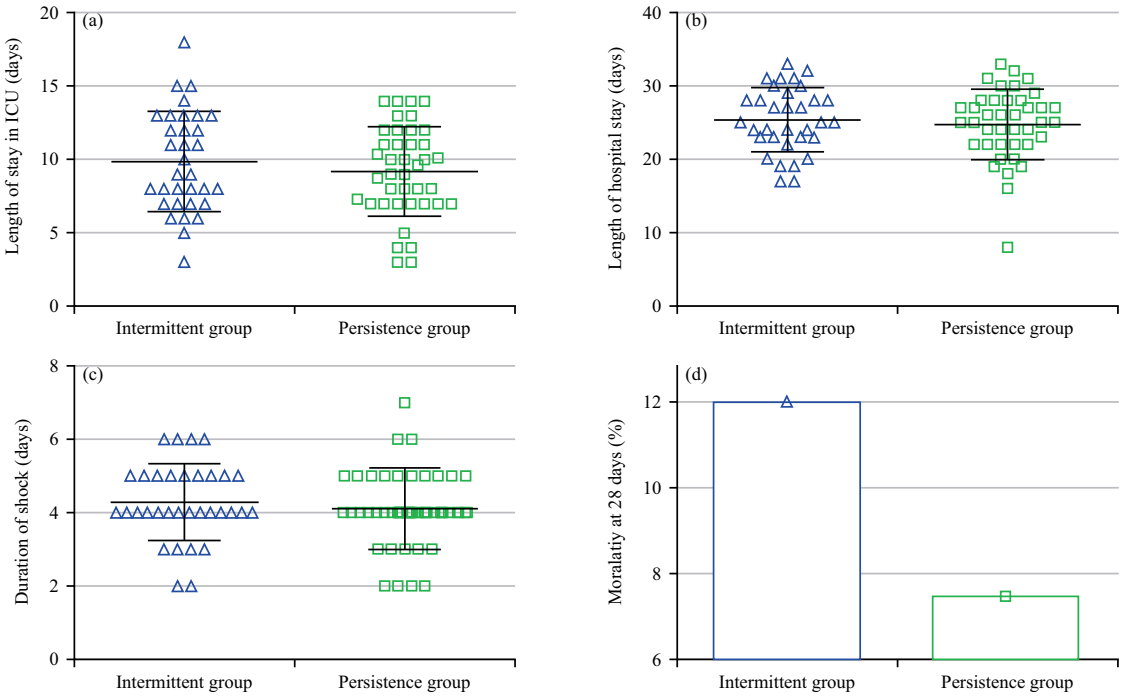

Fig. 4(a-d): Comparison of prognostic-related indicators between continuous and intermittent hydrocortisone treatment in septic shock patients. There were no statistically significant discrepancies between the continuous and intermittent groups in terms of (a) ICU length of stay, (b) Length of hospital stay, (c) Duration of shock and (d) 28 days morbidity and mortality rates

The degree of blood glucose fluctuation is closely associated with the prognosis of septic shock patients, with larger fluctuations inducing hypoglycemia, aggravating mitochondrial damage, enhancing oxidative stress, activating the coagulation system, promoting monocyte adhesion to endothelial cells, triggering endothelial cell apoptosis, increasing capillary leakage and thereby adversely affecting the prognosis[19]. The data from this study demonstrated reduced mean blood glucose (MBG), large amplitude of glycemic excursions (LAGE), hyperglycemic time window and glucose variability (GV) in the continuous group compared to the intermittent group, indicating that continuous hydrocortisone treatment can effectively curb blood glucose fluctuations and improve prognosis.

Inflammatory responses play a critical role in the pathogenesis of septic shock and a surge in inflammatory cytokines like procalcitonin (PCT), Hypersensitive C-Reactive Protein (hs-CRP), Interleukin (IL-1β, IL-6), Tumor Necrosis Factor-Alpha (TNF-α) and High Mobility Group Protein B-1 (HMGB-1) leads to vascular endothelial cell function impairment and microcirculatory disorders, thereby precipitating multi-organ dysfunction[20,21]. Current findings showed significantly reduced levels of these inflammatory markers in both groups 96 hrs post-treatment, particularly in the continuous group, suggesting that continuous hydrocortisone treatment can efficiently dampen the inflammatory response, alleviate vascular endothelial cell function impairment and thus ameliorate the patient's condition[22].

Assessment of T-lymphocyte subset levels effectively reflect the body's immune function[23]. The present study observed significantly higher $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ levels in both groups 96 hrs post-treatment, particularly in the continuous group, while $CD8^+$ levels were significantly lower, especially in the continuous group. This signifies that continuous hydrocortisone treatment can effectively boost immune function and facilitate patient recovery in septic shock.

CONCLUSION

In summary, continuous hydrocortisone treatment for septic shock presents a higher efficacy than intermittent treatment in terms of diminishing blood glucose fluctuations,

modulating oxygen metabolism, suppressing inflammatory response and bolstering immune function. Nonetheless, the benefits in terms of hemodynamics and short-term prognosis remain uncertain. It is important to note that the conclusions drawn from this study are based on a relatively small number of cases and a short study duration. Thus, larger scale studies with extended durations are warranted to further verify these findings.

SIGNIFICANCE STATEMENT

Immune dysfunction and inflammatory response are closely related to the pathogenesis of septic shock. Hydrocortisone demonstrates superior therapeutic efficacy in sepsis and septic shock. In this study, it was found that compared with intermittent hydrocortisone administration, continuous hydrocortisone treatment demonstrated superior efficacy in managing septic shock. The continuous regimen notably mitigated blood glucose variability, regulated oxygen metabolism, suppressed inflammatory responses and enhanced immune functionality. These findings may provide the theoretical basis for the treatment of septic shock.

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