

Insulin therapy is not associated with improved clinical outcomes in critically ill infants with stress hyperglycemia

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Abstract. The aim of the present study was to examine the benefits of insulin use and non-use in critically ill infants with stress-induced hyperglycemia. The present retrospective study used clinical data from 302 critically ill infants with stress hyperglycemia admitted to pediatric intensive care units (PICUs). The patients were recruited randomly and divided into three groups: The tight glycemic control, conventional insulin therapy and control groups. Correlations between insulin therapy and improved clinical outcomes were assessed according to key parameters (length of PICU stay, total length of stay, occurrence of organ dysfunction and mortality). Correlations between blood glucose level and these parameters in the three groups were also examined. Blood glucose levels following insulin therapy were not correlated with the length of PICU stay, total length of stay, mortality, secondary coma, or secondary hepatic or renal dysfunction in the three groups. At 96 h following PICU admission, blood glucose levels were statistically similar (5.0 ± 1.2 , 4.9 ± 1.3 and 5.1 ± 0.9 mmol/l, respectively; $P > 0.05$). Insulin therapy was revealed to have no benefit on the length of hospitalization, the occurrence of organ dysfunction or mortality in critically ill pediatric patients with stress hyperglycemia. Even with no insulin use, the blood glucose level could spontaneously return to normal, with no associated risk of organ dysfunction or fatality.

Introduction

Critically ill patients typically have high blood glucose levels, which is a stress indicator for patients with no history

of diabetes (1-6). High blood glucose levels need to be controlled (2,7-13). Various studies have demonstrated that tight glycemic control (TGC) can reduce the risk of mortality and complications, as well as have other benefits. Tran *et al* (14) and Pham *et al* (15) reported that TGC is necessary in children with severe burns. A prospective randomized trial revealed that it can reduce the risk of mortality in patients with sepsis (5). Vlasselaers *et al* (16) indicated that intraoperative TGC can protect the myocardium and reduce infection in neonatal patients with severe heart disease. Furthermore, Day *et al* (17) revealed that TGC benefits critically ill pediatric patients with meningococcal sepsis. In addition, a study conducted at Leuven University in Belgium indicated that intensive insulin therapy (i.e., TGC) can reduce mortality in critically ill adult and pediatric patients (9,18). However, the optimal blood glucose control target for critically ill children remains uncertain, and some researchers have questioned proposed glucose control targets and, more generally, the benefit of TGC (19-21). In the present study, the characteristics of pediatric patients at first admission were examined, and the effects of blood glucose control [TGC, conventional insulin therapy (CIT) and no insulin] were analyzed using data from critically ill children. The length of stay in the pediatric intensive care unit (PICU), total length of hospitalization, mortality, occurrence of secondary coma, development of secondary hepatic or renal dysfunction, incidence of hypoglycemia and blood glucose reduction were compared among groups. Furthermore, correlations between blood glucose levels and mortality, secondary coma, and secondary hepatic and renal dysfunction following insulin therapy were examined. Blood glucose levels were observed at the time of PICU admission and 24, 48, 72 and 96 h thereafter in the TGC, CIT and control groups. Overall, the benefits of blood glucose control and non-use of insulin therapy were evaluated and the spontaneous resolution of the blood glucose level without insulin therapy was assessed. The study findings suggested that the blood glucose level could return to normal spontaneously, without insulin therapy and with no associated risk, in critically ill pediatric patients with stress hyperglycemia.

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Materials and methods

Ethics and written informed consent. The Ethics Committee of the Shunde Women's and Children's Healthcare Hospital

(Foshan, China) approved the present study. Prior to the start of the research, written informed consent was obtained from next of kin, carers and/or guardians on behalf of the children enrolled in the study.

Study population. All subjects included in the present study were admitted to the Shunde Women's and Children's Healthcare Hospital and Yuexiu District Children's Hospital of Guangzhou between June 2009 and June 2017. Clinical data was collected from 302 critically ill infants with hyperglycemia who were admitted to the hospitals' PICUs. The following data were extracted from patient medical records: Patient age (range, 1-12 months), sex (male, $n=156$; female, $n=146$), diagnosis (22), history of diabetes, steroid use, nutrition delivery, SOFA-associated indicators, length of PICU stay, total length of hospitalization, mortality, occurrence of secondary coma, development of secondary hepatic and renal dysfunction, incidence of ketoacidosis, blood glucose level at PICU admission and change in blood glucose level (at 24, 48, 72 and 96 h), blood ketone level, urine ketone response and blood pH values at first admission and at 24, 48, 72 and 96 h. Eligible subjects met the following criteria: i) Critically ill infants (aged, 1 to 12 months) with stress hyperglycemia; ii) patients examined had with no past history of diabetes (considering both parents); and iii) patients examined had recorded steroid use prior to recruitment.

Patient evaluation. Sepsis and septic shock were evaluated using the Sequential (Sepsis-Related) Organ Failure Assessment (SOFA) and defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) (23). Stress hyperglycemia was defined according to the American Diabetes Association's Diabetes in Hospitals Writing Committee Guidelines (fasting blood glucose ≥ 7.0 mmol/l or random blood glucose ≥ 11.1 mmol/l) (22). Severe hyperglycemia was defined as a blood glucose level ≥ 25.00 mmol/l at first admission (22). Secondary coma, secondary hepatic dysfunction and secondary renal dysfunction in patients with sepsis were defined according to the Sepsis-3 (23). Secondary coma was defined as a Glasgow score < 8 following hospitalization; secondary hepatic dysfunction was defined as a total bilirubin level > 4 mg/dl (72 mmol/l) or alanine aminotransferase level of at least two times the upper limit of the normal level for the patient's age; and secondary renal dysfunction was defined as a serum creatinine level of at least two times the upper limit of the normal level for the patient's age or a 2-fold increase in the baseline creatinine level during the PICU stay. Hypoglycemia was defined as a blood glucose level < 2.8 mmol/l, and severe hypoglycemia was defined as a level ≤ 2.2 mmol/l (24). Ketoacidosis was defined according to the International Society for Pediatric and Adolescent Diabetes biochemical criteria as a blood glucose level > 11 mmol/l and venous pH < 7.3 following hospitalization, and presence of ketonemia and ketonuria (25,26).

Grouping method. The patients were into three groups: TGC ($n=85$), CIT ($n=89$) and control (no insulin use; $n=128$) groups. Blood glucose control points were as follows: < 6.1 to 4.4 mmol/l for the TGC group and 10.0 mmol/l or less per liter (4,9) for the CIT group. Insulin administration was

stopped in the two groups when the target range was reached. Patients who did not receive insulin therapy were assigned to the control group.

Insulin therapy and nutritional support treatment. Continuous short-acting insulin infusion was delivered with a micropump. The insulin dose was 0.5 - 1 IU/kg·day, and was adjusted according to the blood glucose level. Blood glucose levels were measured with a bedside glucose meter (Free Style Optium Neo; model XEMV168-026F; Abbott Diabetes Care Ltd., Chicago, IL, USA) every 30 min following insulin adjustment. Enteral nutrition was initiated as early as possible for all patients. Nutrition standards were established according to nutritional support treatment guidelines (27), with total calories set to 20 - 30 kcal·kg⁻¹·24 h⁻¹ (nitrogen, 0.08 - 0.25 g·kg⁻¹·24 h⁻¹; 20 - 40% fat emulsion).

Statistical analyses. Statistical analyses were performed with SPSS statistical software (version 17.0; SPSS, Inc., Chicago, IL, USA). Figures were generated using GraphPad software (La Jolla, CA, USA; version 5.01). $P < 0.05$ was considered to indicate a statistically significant difference. Kolmogorov-Smirnov testing was used to investigate the distribution of blood glucose levels in the TGC, CIT and control groups. The results indicated that these distributions were normal ($Z=0.935$, $P=0.080$; $Z=0.912$, $P=0.088$; and $Z=0.917$, $P=0.091$, respectively). The χ^2 test was used for intergroup comparison of count data (sex, mortality, secondary coma, secondary hepatic dysfunction, secondary renal dysfunction and incidence of hypoglycemia). Age, SOFA score, length of PICU stay, total length of hospitalization, and blood glucose levels at PICU admission and thereafter were presented as the mean \pm standard deviation. Results were compared between multiple groups using one-way ANOVA, while a Neuman-keuls test was applied to compare differences among these groups. Pearson's test was applied to examine correlations between blood glucose levels following insulin therapy and mortality, secondary coma, and secondary hepatic and renal dysfunction in all patients.

Results

A total of 302 patients (156 male patients and 146 female patients), with a mean age at enrollment of 7 months (range, 1 to 12 months), were assessed in the present study. Patients had the following diseases: Sepsis ($n=67$), septic shock ($n=23$), severe pneumonia ($n=120$), meningoencephalitis ($n=28$), acute lung hemorrhage ($n=18$), acute laryngeal obstruction ($n=11$), persistent asthma ($n=10$), acute myocarditis ($n=11$), acute nephritis ($n=8$) and necrotic enteritis ($n=6$). Among critically ill patients with stress hyperglycemia in the TGC ($n=85$), CIT ($n=89$) and control ($n=128$) groups, these venous blood glucose levels did not differ significantly between male ($n=156$) and female patients ($n=146$; 14.7 ± 1.9 and 14.6 ± 1.8 mmol/l respectively; $P > 0.05$; Table I). No patient had severe stress hyperglycemia (blood glucose level > 25.00 mmol/l). There was not significant difference in mean venous blood glucose levels at first admission (15.2 ± 3.8 , 14.6 ± 4.5 and 14.2 ± 4.7 mmol/l, respectively; $P > 0.05$; Table II, Fig. 1). Certain characteristics of pediatric patients at first administration did not

Table I. Blood glucose levels at first admission according to pathology and sex.

Factor	Total		Male		Female	
	n	Blood glucose (mmol/l)	n	Blood glucose (mmol/l)	n	Blood glucose (mmol/l)
Disease						
Sepsis	67	15.0±1.6	35	15.1±1.1	32	14.8±2.1
Septic shock	23	16.7±2.0	12	16.8±2.0	11	16.5±1.9
Severe pneumonia	120	14.7±1.5	62	14.6±1.2	58	14.8±1.7
Meningoencephalitis	28	14.1±1.8	13	14.1±1.5	15	14.0±2.1
Acute lung hemorrhage	18	15.0±1.4	10	15.1±1.1	8	14.8±1.7
Acute laryngeal obstruction	11	14.5±1.5	6	14.8±1.3	5	14.1±1.7
Persistent asthma	10	13.1±1.6	6	13.0±1.5	4	13.1±1.7
Acute myocarditis	11	13.4±1.9	5	12.7±2.3	6	14.0±1.5
Acute nephritis	8	12.6±1.5	4	12.5±1.4	4	12.7±1.6
Necrotic enteritis	6	13.6±1.6	3	13.1±2.1	3	14.0±1.1
Disease total	302		156	14.7±1.9	146	14.6±1.8

Total male vs. female: $\chi^2=1.23$, $P=0.71$; total blood glucose: $F=0.3$, $P=0.68$.

Table II. Characteristics of patients at first admission.

Variable	TGC group	CIT group	Control group	P-value
Number of subjects	85	89	128	-
Age (months)	7±4.9	7±4.5	7±4.6	0.22
Male (%)	51.66	52.54	51.44	0.71
Blood glucose, mmol/l	15.2±3.8	14.6±4.5	14.2±4.7	0.66 ^a , 0.69 ^b and 0.67 ^c
Arterial oxygen saturation, %	81±11.5	80±21.4	82±20.1	0.29
PaO ₂ /FI O ₂ , kPa	28.7±15.7	30.5±14.3	29.6±12.7	0.30
Systolic blood pressure, mmHg	71±15.2	70±86.4	73±35.6	0.19
MAP, mm Hg	51±18.2	53±11.5	51±17.7	0.32
pH value	7.2±0.2	7.2±0.5	7.2±0.4	0.59
Hemoglobin, g/l	87±17	89±35	89±24	0.26
Platelet, 10×10 ⁹ /l	9.1±0.7	9.0±0.3	9.0±0.6	0.32
Total bilirubin, μmol/l	19±8.7	18±9.4	19±11.8	0.25
ALT, U/l	39±19	37±15	37±2	0.27
Creatinine, mg/dl	1.1±0.8	1.0±0.7	1.0±0.5	0.30
C-reactive protein, mg/l	49±22.7	47±19.0	47±27.4	0.26
Procalcitonin, mg/l	3±1.1	3±1.4	3±1.3	0.49
Blood lactic acid, mmol/l	3±0.9	3±1.1	3±1.2	0.53
Urine volume, ml/kg·h	0.6±0.3	0.6±0.1	0.6±0.3	0.97
GCS, score	10±2.2	10±2.7	10±2.6	0.54
SOFA, score	8.67±3.14	8.79±2.55	8.80±2.61	0.28

^aTGC group vs. the CIT group; ^bTGC group vs. the control group; ^cCIT group vs. the control group. TGC, tight glycemic control; CIT, conventional insulin therapy; PaO₂/FI O₂, oxygenation index; MAP, mean arterial pressure; ALT, alanine aminotransferase; GCS, Glasgow Coma Scale; SOFA, Sequential (Sepsis-Related) Organ Failure Assessment.

differ among groups (Table II), including age, male sex, blood glucose, arterial oxygen saturation, PaO₂ /FI O₂, systolic blood pressure and MAP.

Length of PICU stay and total length of hospitalization were shorter in the TGC group when compared with the CIT

and control groups; however this difference was not significant ($P>0.05$). Mortality and the occurrence of secondary coma, secondary hepatic dysfunction and secondary renal dysfunction did not significantly differ among groups ($P>0.05$). At 24, 48 and 72 h, blood glucose levels in TGC, CIT and

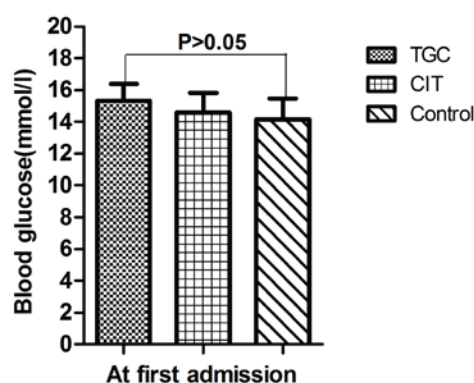


Figure 1. At first admission, blood glucose levels in the TGC, CIT and control groups were 15.2 ± 3.8 , 14.6 ± 4.5 , and 14.2 ± 4.7 mmol/l, respectively. The differences were not significant ($P > 0.05$). TGC, tight glycaemic control; CIT, conventional insulin therapy.

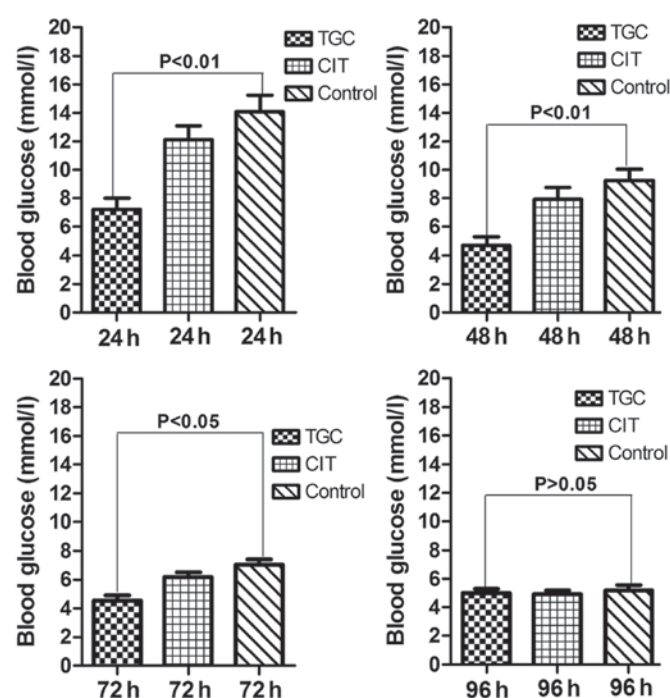


Figure 2. At 24 and 48 h following admission, blood glucose levels in the TGC, CIT and control groups were 7.4 ± 2.5 , 11.2 ± 3.8 , and 14.5 ± 4.1 mmol/l ($P = 0.007$, $P < 0.01$) and 4.8 ± 2.6 , 7.9 ± 2.5 and 9.5 ± 3.5 mmol/l ($P = 0.008$, $P < 0.01$), respectively; these levels at 72 and 96 h were 4.7 ± 1.5 , 6.3 ± 1.1 and 6.8 ± 1.7 mmol/l ($P = 0.039$, $P < 0.05$) and 5.0 ± 1.2 , 4.9 ± 1.3 and 5.1 ± 0.9 mmol/l ($P > 0.05$), respectively. TGC, tight glycaemic control; CIT, conventional insulin therapy.

control groups differed significantly [7.4 ± 2.5 , 11.2 ± 3.8 and 14.5 ± 4.1 mmol/l ($P < 0.01$); 4.8 ± 2.6 , 7.9 ± 2.5 and 9.5 ± 3.5 mmol/l ($P < 0.01$); and 4.7 ± 1.5 , 6.3 ± 1.1 and 6.8 ± 1.7 mmol/l ($P < 0.05$), respectively]. No significant difference between groups was noted at 96 h (5.0 ± 1.2 , 4.9 ± 1.3 , and 5.1 ± 0.9 mmol/l, respectively; $P > 0.05$; Fig. 2).

Notably, 5 patients in the TGC group exhibited hypoglycemia [blood glucose range, 2.6–2.10 mmol/l: 2.3, 2.6 and 2.7 mmol/l in 3 (3.53%) patients; and severe hypoglycemia (2.10 and 2.15 mmol/l) in 2 (2.35%) patients] following 26, 29, 38, 43 and 47 h of insulin therapy, respectively. The incidence of hypoglycemia was 5.88%. No patient in the CIT

or control group exhibited hypoglycemia. Comparison of the incidence of hypoglycemia between multiple groups was significantly different ($\chi^2 = 15.62$, $P < 0.01$; Table III). During the entire administration period, blood glucose levels were not correlated with mortality, secondary coma, hepatic dysfunction or renal dysfunction (Table IV).

Ketone was not detected upon exhaled breath in patients, and blood ketosis and urine ketone response results were negative. At first admission and at 24, 48, 72 and 96 h, pH values in the TGC, CIT and control groups did not differ significantly ($P > 0.05$; Table V).

Discussion

Stress hyperglycemia and insulin resistance are common in critically ill patients, particularly those with sepsis (3,28). Multiple pathogenetic mechanisms are responsible for this metabolic syndrome; however, increased release of pro-inflammatory mediators and counter-regulatory hormones may serve a pivotal role (28). This process leads to accelerated catabolism and strengthened dysplasia function of glucose, which in turn results in stress hyperglycemia (28). This condition is caused by a decrease in insulin secretion under stress and represents a temporary state of insulin resistance and concomitant relative insulin deficiency (3–6). In early studies, Van den Berghe *et al* (9) proposed the use of insulin therapy for TGC (blood glucose level < 6.1 mmol/l) to reduce mortality and complications in critically ill patients in surgical ICUs. Reports have indicated that this application of insulin therapy can shorten the PICU stay and reduce the mortality, infection and organ dysfunction rates in critically ill patients with stress hyperglycemia (5,9,13,15–17,29,30). However, other studies have documented advantages of freestyle glycaemic control using insulin (24,31). The use of TGC is controversial. For example, a study conducted at Leuven University demonstrated beneficial responses to TGC (9), but follow-up studies could not confirm these results (18,20,21,32). Furthermore, a systematic review and network meta-analysis of randomized controlled trials revealed no benefit of TGC with regard to the length of hospitalization or death in critically ill patients (8). The persisting disparities in results reflect the difficulty of replicating such research.

Severe stress hyperglycemia (blood glucose level > 25.00 mmol/l) was observed in no patients (0.00%) in the present sample; 100% of patients had mild to moderate stress hyperglycemia. This high blood glucose state seems to cause limited harm to the body, but information on this issue is limited. In the present study, no significant difference in the length of PICU stay or total length of hospitalization among the TGC, CIT and control groups was indicated. In addition, no correlation between the blood glucose level and mortality, occurrence of secondary coma, or development of secondary hepatic dysfunction and renal dysfunction was indicated following treatment. These findings suggest no superiority of TGC over other approaches, which is in agreement with previously reported results (8,20). Thus, the present findings did not demonstrate a benefit of insulin therapy or risk associated with its non-use. Although we are not aware of previous reports on the latter, the present retrospective study demonstrated that transient mild to moderate stress hyperglycemia does not typically cause harm and does not necessitate insulin therapy.

Table III. Comparison of data from the TGC, CIT and control groups.

Variable	N	PICU length of stay (day)	Total length of stay (day)	Mortality n (%)	Secondary coma n (%)	Secondary hepatic dysfunction n (%)	Secondary renal dysfunction n (%)	Hypoglycemia n (%)
Groups								
TGC	85	5±2.4	11±8.6	10 (11.76)	5 (5.38)	7 (7.53)	6 (7.06)	5 (5.88)
CIT	89	5±8.9	11±1.2	11 (12.36)	5 (5.62)	8 (7.84)	8 (7.84)	0 (0.00)
Control	128	6±1.8	12±1.7	15 (11.72)	7 (5.47)	11 (8.59)	9 (7.03)	0 (0.00)
χ^2		1.16	1.27	1.25	0.83	0.97	1.04	15.62
P-value		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	<0.01
		P>0.05	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05	^{a,b} P<0.01 ^c P>0.05

^aTGC group vs. the CIT group; ^bTGC group vs. the control group; ^cCIT group vs. the control group. TGC, tight glycemic control; CIT, conventional insulin therapy; PICU, pediatric intensive care unit.

Table IV. Correlations of blood glucose levels with correlative factors during the entire administration period in the TGC, CIT and control groups.

Correlative factor	Pearson's test		F test		R2
	r	P-value	F	P-value	
Mortality	0.171	0.12	19.315	0.11	0.154
Coma	0.150	0.09	17.713	0.10	0.148
Hepatic dysfunction	0.166	0.10	18.431	0.11	0.148
Renal dysfunction	0.156	0.11	19.376	0.12	0.154

TGC, tight glycemic control; CIT, conventional insulin therapy.

Table V. pH values in the TGC, CIT and control groups.

Groups	pH values				
	At first	24 h	48 h	72 h	96 h
Group					
TGC	7.2±0.2	7.3±0.1	7.3±0.2	7.4±0.2	7.4±0.2
CIT	7.2±0.5	7.3±0.1	7.3±0.2	7.4±0.2	7.4±0.2
Control	7.2±0.4	7.3±0.2	7.3±0.1	7.4±0.1	7.4±0.1
F	0.29	0.32	0.29	0.29	0.29
P-value	>0.05	>0.05	>0.05	>0.05	>0.05

TGC, tight glycemic control; CIT, conventional insulin therapy.

The results of the study suggest that the blood glucose level can spontaneously return to normal as the severe inflammatory reaction subsides and the patient's condition improves. Marik and Raghavan (28) indicated that only persistently high blood glucose levels can cause organ damage. In the control group in the present study, blood glucose levels had dropped to 9.5±3.5 mmol/l at 48 h following PICU admission,

were 6.8±1.7 mmol/l at 72 h, and were considered normal (5.2±0.9 mmol/l) at 96 h. However, further investigation is required to confirm these findings.

The present observation of hypoglycemia following therapy in 5 patients in the TGC group (severe in 2 cases) is in agreement with the results of a meta-analysis, which documented an increased risk of hypoglycemia that was associated

with target blood glucose levels <110 mg/dl (6.1 mmol/l) (20). Although no correlation between the blood glucose level and mortality or other complications was identified, the potential risk of hypoglycemia associated with the deterioration of patients' conditions cannot be excluded. Studies with larger samples may help to clarify this issue.

Ketoacidosis generally occurs in children aged <5 years with type I diabetes and low levels of effective insulin action (29,33). In the present study, no evidence of this condition was indicated, even in patients who received no insulin therapy. Due to its transient nature, stress hyperglycemia may not cause ketoacidosis in non-diabetic patients (4).

Insulin therapy revealed no benefit in terms of the length of hospitalization or risk of organ dysfunction or fatality, and thus was not associated with improved clinical outcomes in critically ill infants with stress hyperglycemia. Even without insulin therapy, the blood glucose level may spontaneously return to normal with no associated risk. However, further prospective randomized controlled trials are required to confirm the findings of the present study.

The mechanisms why insulin therapy exhibited no benefit in pediatric patients with stress hyperglycemia in the present study remain clear. Because this is a retrospective study, all patients lacked data regarding insulin, c-peptide response and inflammatory factors. Future prospective randomized controlled trials will explore these mechanisms.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FW and YZ conceived and designed the experiments of the current study. YZ, CL, MD and JfZ performed the experiments. FW and JfZ analyzed the data. JpZ contributed reagents/materials/analysis tools. FW and CL wrote the manuscript.

Ethics approval and consent to participate

The current study was approved by the ethics committee of the Shunde Women and Children's Healthcare Hospital (Foshan, China).

Patient consent for publication

All parents and guardians of the children enrolled in the current study provided written informed consent.

Competing interests

The authors declare that they have no competing interests.

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