Well perioperative glycemic control improves outcomes in neonates with surgical necrotizing enterocolitis in a tertiary referral center: a retrospective study

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Abstract

Background: Necrotizing enterocolitis (NEC) is one of the most common and devastating diseases that occurs in neonates, and often requires surgical intervention. Hyperglycemia or hypoglycemia can easily occur in newborns, due to their metabolic immaturity. It remains unknown how factors associated with anesthesia especially perioperative glucose level affect the surgical outcomes of neonates with NEC. In this retrospective observational study, we analyzed the risk factors associated with prolonged hospitalization among neonates who received surgical treatment for necrotizing enterocolitis.

Methods: From January 2016 to October 2019, a total of 204 infants with a gestational age of 28 weeks to 40 weeks underwent open surgery for NEC at Shengjing Hospital of China Medical University. Among those infants, 111 patients were assigned to the well glycemic control group and 93 patients were assigned to the poor glycemic control group. The primary study outcome was the length of postoperative hospital stay. Risk factors that may affect surgical outcomes were collected and analyzed via multivariate logistic regression to determine their association with postoperative hospital stay.

Results: A multivariate logistic regression analysis showed that high preoperative weight (OR=0.995, 95%CI=0.992-0.997, p<0.001) and well glycemic control (OR=0.129, 95%CI=0.031-0.535, p=0.005) were independent protective factors for prolonged hospital stay, whereas long duration of endotracheal intubation in NICU(OR=1.239, 95%CI=1.016-1.512, p=0.035) and long days of antibiotics use (OR=1.421, 95%CI=1.233-1.637, p<0.001) were independent risk factors for prolonged hospital stay. Patients with perioperative blood glucose control within the prespecified range(47-150mg/dL) had shorter postoperative hospital stays than those with perioperative blood glucose measurements outside those limits (22 [18,26] vs 29 [24.5,36.5] days, p <0.001).

Conclusions: Perioperative glucose levels outside a pre-specified range were an independent risk factor for a prolonged hospital stay in a population of neonates who underwent surgical repair for NEC.

Introduction

Necrotizing enterocolitis (NEC) is one of the most common and devastating gastrointestinal inflammatory diseases that occurs in preterm infants. Its mortality rate can be up to 30%, and the afflicted infants often require surgery.[1, 2] NEC is characterized by partial or full thickness intestinal ischemia, usually in the terminal ileum, but may involve the entire bowel.[3] The initial treatments for NEC include fluid infusion, ventilator support, antibiotic therapy, and other non-surgical methods. However, progressive NEC is treated by the surgical installation of peritoneal drains, bowel resection, and creation of an ostomy.[4] Pathoglycemia is common in critically ill neonates. The high metabolic rate, low glycogen storage rate, and impaired gluconeogenesis and ketogenesis in neonates especially in preterm babies place them at a higher risk for hypoglycemia, which may be associated with brain injury.[5, 6] Under stress, derangements in glucose homeostasis may lead not only to hypoglycemia but may also manifest in hyperglycemia especially in the setting of glucose infusions exceeding their normal glucose turnover rate due to an immature response to pathoglycemia. Furthermore, premature infants are more likely to display absolute or relative insulin

deficiency or insulin resistance. Hyperglycemia has been identified as a risk factor for poor wound healing and surgical site infections, which may cause early death and morbidity, and was especially related to intracranial hemorrhage in extremely low birth weight infants.[7-9] The additional stress of surgery and anesthesia may exacerbate already deranged glucose homeostasis associated with bowel ischemia. Glucose variability is the extent of blood glucose fluctuations which occur within a specified period. Hence, perioperative glucose oscillations are common in neonates, and careful blood glucose monitoring and management is crucial for neonates undergoing surgery. Less is known of the normal range of glucose for neonates. A cohort study by Mckinlay found that neonatal hypoglycemia was not associated with an adverse neurologic outcome when treatment was provided to maintain a blood glucose concentration of at least 47 mg/dl.[10] Hays suggested that glucose value >150mg/dL is a risk factor for early death and morbidity in extremely low birth-weight infants and will increase the risk of cerebral hemorrhage.[11] However, a few study shows that tight glucose control of neonates may lead to high risk of hypoglycemia which was more severe and maintaining glucose <144 mg/dl (8mmol/L) has not consistently demonstrated improvement in outcomes.[12, 13]. Few studies focused on blood glucose level and glucose variability on the effect of prognosis in critical ill neonates especially in perioperative period. We have observed a number of NEC neonates who suffered from hypoglycemia, hyperglycemia and glucose variability in our care. This retrospective study was designed to assess the association between perioperative blood glucose control within a range of 47-150 mg/dL and the length of postoperative hospital stay among neonates who received surgical treatment for necrotizing enterocolitis.

Materials And Methods

Ethics approval

The study protocol was approved by the Clinical Research Ethics Committee of China Medical University, Shengjing Hospital (2018PS515K). The initial IRB (institutional review board) approval is dated November 22, 2018. Due to the retrospective nature of this study, and the fact that all pertinent data had been obtained from patient medical records, the local Ethics Committee agreed that the study did not require written informed consents.

Patients and inclusion/exclusion criteria

Potential participants were patients who had undergone open abdominal surgery for necrotizing enterocolitis, as diagnosed by a preoperative X-ray assessment, clinical symptoms, an intraoperative diagnosis, and then subsequently confirmed by a surgeon at the China Medical University from January 2016 to October 2019. All patients met the stage Ⅱ NEC surgical criterion: medical therapy was not successful for 48 hours prior to surgery.[14] Patients who met any of the following criteria were excluded from the study: (1) gestational age < 28 weeks; (2) surgery was performed in a manner other than open abdominal bowel resection and ostomy; (3) fewer than 5 glucose measurements in the perioperative period; (4) NEC was accompanied by a severe congenital heart disease, or other significant co-morbidity; (5) refused treatment before meeting the clinical cure standard or died after surgery. Infants with a tiny-to-small patent ductus arteriosus or patent foramen ovale were not considered to have congenital heart disease and

were therefore included.[15] Among 309 patients who underwent open abdominal surgery from January 2016 to October 2019, a total of 204 patients met the study's inclusion/exclusion criteria. Those patients were divided into two groups according to their perioperative blood glucose level. Patients with a perioperative blood glucose concentration in the range of 47–150 mg/dL were designated as well glycemic control. Any two measurements (consecutive or non-consecutive) of blood glucose made 24 hours before, during or after the surgery, and whose values were not within the pre-specified range, were considered to indicate poor perioperative glycemic control. As a result, 111 patients were assigned to the well glycemic control group and 93 patients were assigned to the poor glycemic control group. All blood glucose values were determined by arterial puncture or the finger/heal stick blood glucose test. Prior to surgery, all newborns with NEC underwent the same routine treatment, which included bowel rest, intravenous nutrition, parenteral antibiotics, nasogastric suction, and cardio-respiratory support as necessary.

Anesthesia, surgery, and perioperative management

All patients received general anesthesia via endotracheal intubation. Anesthesia was induced with sevoflurane (6–8%) and maintained with sevoflurane (2.5-3%) or sevoflurane combined with remifentanil (0.05–0.2 μg/kg/min) and inotropic agents when necessary. Intraoperative fluid maintenance consisted of normal saline solution or 1% or 5% glucose-containing solution to achieve a plasma glucose level of 47–150 mg/dL.[16] Insulin therapy (0.01–0.2 U/(kg·h) was given to patients whose hyperglycemia persisted despite the decrease of glucose infusion. Patients were actively warmed throughout surgery. Bowel resection and ostomy were performed routinely. Postoperative length of stay (LOS) were recorded according to the hospital's discharge chart. All procedures were performed by qualified surgeons and anesthesiologists who each had > 10 years of clinical experience.

Data collection

Data were collected from the hospital's medical record system, and eligible patients were identified via the study's inclusion/exclusion criteria. Demographic characteristics (gender, gestational age, gestational weight, type of delivery), pre-operative information (post-conceptual age, use of inotropic agents, glucose delivery rate(GDR), weight before surgery, hemoglobin, heart rate, blood pressure, albumin, creatinine, CRP, American Society of Anesthesiologists(ASA) classification, entry into the operating room (O.R.) with an endotracheal tube), intraoperative information (surgery duration, anesthesia duration, blood loss, blood transfusion, fluid balance, hemodynamic fluctuations, extubated time), and postoperative information (hemoglobin, albumin, occurrence of complications, antibiotics use, length of hospital stay, standard deviation (SD) of blood glucose) were all included in the patient records. The primary outcome of the study was the length of postoperative hospital stay, which is a comprehensive indicator reflecting the prognosis of neonatal NEC.

Statistical analysis

Numeric data with a normal distribution were compared using the independent samples t test; numeric data with a non-normal distribution were compared using the Mann-Whitney U test; categorical data were compared by using the chi-square test or Fisher's exact test. To identify independent risk factors for

postoperative hospital stay, variables with a p-value ≤ 0.1 in univariate analyses were included in a multivariate logistic model. A two-sided p-value < 0.05 was considered to be statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 software (IBM Corp., Armonk, NY, USA).

Results

Patients

204 eligible admissions generated 1264 glucose values (median: 108 mg/dL; range: 34–245 mg/dL). A total of 309 infants with NEC underwent surgery during the study period. Among those patients, 105 were excluded for the following reasons: 18 were of age < 28 weeks; 9 patients were complicated with severe congenital heart disease; 22 patients did not receive bowel resection and enterostomy; 23 patients refused treatment before meeting the clinical cure standard or died after surgery; 26 patients had fewer than 5 glucose measurements; 7 patients had insufficient data. Consequently, data from 204 patients was collected for analysis (Fig. 1).

The baseline and perioperative data are presented in Table 1 and outcome variables are presented in Table 2.

Table 1
Pre-, intra- and postoperative variables in the study population

	Totally	WGCG	PGCG	P value
Variable	**(n = 204)**	**(n = 111)**	**(n = 93)**	
Gender				0.261
Male	132(64.7%)	68(61.3%)	64(68.8%)	
Female	72(35.3%)	43(38.7%)	29(31.2%)	
Gestational age(weeks)	31.91 ± 2.63	32.21 ± 2.54	31.56 ± 2.71	0.077
Gestational weight(g)	1725.15 ± 550.03	1795.16 ± 567.22	1643.78 ± 519.86	0.05
Type of delivery				0.345
caesarean delivery	147(72.1%)	83(74.8%)	64(68.8%)	
natural labor	57(29.9%)	28(25.2%)	29(31.2%)	
Post-conceptual age (weeks)	36.01 ± 3.65	36.50 ± 4.12	35.41 ± 2.91	0.028
Preoperative weight(g)	2003.02 ± 510.05	2054.14 ± 563.57	1942.02 ± 432.86	0.118
Preoperative hemoglobin(g/l)	115.35 ± 22.80	114.59 ± 22.46	116.27 ± 23.30	0.601
Preoperative albumin (g/l)	29.46 ± 4.65	29.29 ± 4.93	29.67 ± 4.31	0.557
Preoperative creatinine (g/l)	47.85 ± 15.67	45.84 ± 16.17	50.24 ± 14.77	0.045
Preoperative CRP(mg/l)	29.9(6.70,78.83)	32.1(7.12,75.6)	28.9(6.36,83.1)	
Preoperative SBP (mmHg)	65.36 ± 11.46	65.66 ± 12.06	65.00 ± 10.76	0.684
Preoperative DBP (mmHg)	35.06 ± 8.65	35.19 ± 9.56	34.90 ± 7.48	0.815

WGCG = Well Glycemic Control Group. PGCG = Poor Glycemic Control Group. SBP = Systolic Blood Pressure. DBP = Diastolic Blood Pressure. HR = Heart Rate.

O.R. = Operating Room. ASA = American Society of Anesthesiologists. ICU = Intensive Care Unit. GDR = Glucose Delivery Rate. SD = Standard Deviation. BG = Blood Glucose

Data are presented as the mean ± standard deviation, number of patients, or median (interquartile range), unless otherwise indicated.

[a] defined when having met any of the following criteria: systolic pressure ≥ 100 or ≤ 40 mmHg, or increased > 30% above baseline; heart rate ≥ 180 or ≤ 100 bpm.

[b] the blood products infused included packed red blood cells, blood plasma, and platelets.

[c] some of the patients were extubated in the O.R. and some were extubated in the NICU after surgery.

	Totally	WGCG	PGCG	P value
Preoperative HR (bmp)	146.35 ± 12.29	146.4 ± 14.06	146.3 ± 9.86	0.955
Preoperative inotrope drugs				0.781
Yes	39(19.1%)	22(19.8%)	17(18.3%)	
No	165(80.9%)	89(80.2%)	76(81.7%)	
Preoperative nutrition				
GDR one day before surgery(mg/kg/min)	6.83 ± 0.96	6.90 ± 1.03	6.74 ± 0.87	0.226
GDR on the day of surgery(mg/kg/min)	6.59 ± 1.19	6.63 ± 1.30	6.55 ± 1.05	0.648
ASA classification				0.371
2 and 3	136(66.7%)	77(69.4%)	59(63.4%)	
4	68(33.3%)	34(30.6%)	34(36.6%)	
Entry into O.R. with endotracheal tube				0.03
Yes	80(39.2%)	36(32.4%)	44(47.3%)	
No	124(60.8%)	75(67.6%)	49(52.7%)	
Duration of surgery (mins)	89.00 ± 26.87	91.68 ± 26.18	85.80 ± 27.46	0.119
Duration of anesthesia (mins)	107.02 ± 29.37	111.28 ± 29.51	101.94 ± 28.54	0.023
Hemodynamic fluctuation[a]				0.219
Yes	53(26%)	25(22.5%)	28(30.1%)	
No	151(74%)	86(77.5%)	65(69.9%)	

WGCG = Well Glycemic Control Group. PGCG = Poor Glycemic Control Group. SBP = Systolic Blood Pressure. DBP = Diastolic Blood Pressure. HR = Heart Rate.

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[a] defined when having met any of the following criteria: systolic pressure ≥ 100 or ≤ 40 mmHg, or increased > 30% above baseline; heart rate ≥ 180 or ≤ 100 bpm.

[b] the blood products infused included packed red blood cells, blood plasma, and platelets.

[c] some of the patients were extubated in the O.R. and some were extubated in the NICU after surgery.

	Totally	WGCG	PGCG	P value
Blood loss (ml)	5(5,10)	5(2,10)	5(5,10)	
Fluid balance (ml)	20(18.5,40)	20(20,40)	20(15,40)	
Perioperative blood transfusion(ml)	30(0,30)	30(0,30)	25(0,30)	
Perioperative blood transfusion [b]				0.571
Yes	134(65.7%)	71(64%)	63(67.7%)	
No	70(34.3%)	40(36%)	30(32.3%)	
Postoperative hemoglobin(g/l)	104.77 ± 14.43	104.69 ± 13.14	104.87 ± 15.91	0.931
Postoperative albumin (g/l)	35.05 ± 7.32	35.01 ± 7.23	35.10 ± 7.48	0.927
duration of extubation [c]				
time at O.R.(mins)	15(10,20)	15(10,20)	11.50(7,27.5)	
time in ICU (days)	4(3,7)	4(2.75,6)	5(4,8)	
GDR one day after surgery(mg/kg/min)	7.06 ± 0.93	7.15 ± 1.03	6.96 ± 0.80	0.121
Glucose value(mg/dL)	105.29 ± 16.21	100.45 ± 14.99	111.07 ± 15.79	< 0.001
SD of BG(mg/dL)	36.83 ± 10.20	31.01 ± 8.05	43.78 ± 7.91	< 0.001

WGCG = Well Glycemic Control Group. PGCG = Poor Glycemic Control Group. SBP = Systolic Blood Pressure. DBP = Diastolic Blood Pressure. HR = Heart Rate.

O.R. = Operating Room. ASA = American Society of Anesthesiologists. ICU = Intensive Care Unit. GDR = Glucose Delivery Rate. SD = Standard Deviation. BG = Blood Glucose

Data are presented as the mean ± standard deviation, number of patients, or median (interquartile range), unless otherwise indicated.

[a] defined when having met any of the following criteria: systolic pressure ≥ 100 or ≤ 40 mmHg, or increased > 30% above baseline; heart rate ≥ 180 or ≤ 100 bpm.

[b] the blood products infused included packed red blood cells, blood plasma, and platelets.

[c] some of the patients were extubated in the O.R. and some were extubated in the NICU after surgery.

Table 2
Postoperative outcomes

	Totally	WGCG	PGCG	Statistic		Significance
Mann-Whitney U				Z		p
Antibiotic days	17(12,22)	14(10,20)	20(15.5,24.5)	-5.293		< 0.001
Postoperative hospital stay(days)	25(20,32)	22(18,26)	29(24.5,36.5)	-5.34		< 0.001
Chi-Square				χ2	Relative Risk (95%CI)	p
Postoperative hospital stay				25.482	4.646(2.513–8.588)	< 0.001
≤ 28days	130(63.7%)	88(79.3%)	42(45.2%)			
> 28days	74(36.3%)	23(20.7%)	51(54.8%)			
Occurrence of complications [d]				28.548	4.926(2.699–8.991)	< 0.001
Yes	84(41.2%)	27(24.3%)	57(61.3%)			
No	120(58.8%)	84(75.7%)	36(38.7%)			

[d] postoperative complications were defined as new onset medical conditions which impaired the patient's recovery and required therapeutic intervention. These conditions included sepsis, intestinal obstruction, intestinal bleeding, enterostenosis, emesis, diarrhea, respiratory failure, and hypotension.

Our analysis showed that patients in the well glycemic control group and poor glycemic control glucose group had similar values for clinical parameters such as gender, gestational age, gestational weight, ASA, preoperative CRP, glucose delivery rate ($p > 0.05$) (Table 1). The median length of postoperative hospital stay was shorter among patients in well glycemic control group than among patients in poor glycemic control group (22[18, 26] vs 29[24.5,36.5] days, $p < 0.001$). Furthermore, postoperative antibiotics use (14[10, 20] vs 20[15.5,24.5)] days, $p < 0.001$) was shorter and the incidence of complications was lower (24.3% [27/111 patients] vs 61.3% [57/93 patients], $p < 0.001$) in well glycemic control group when compared with the poor glycemic control group.(Table 2)

Risk factor analysis

In order to investigate the risk factors for a prolonged postoperative hospital stay, we compared the clinical characteristics of patients with a ≤ 28 day hospital stay with those of patients with a > 28 day hospital stay (Tables 3,4). A univariate logistic regression analysis identified 14 factors that were associated with the length of a postoperative hospital stay ($p \leq 0.1$); those factors included gestational age, gestational weight,

preoperative creatinine, post-conceptual age, entry into the operating room (O.R.) with an endotracheal tube, preoperative weight, ASA classification, blood loss, hemodynamic fluctuations, duration of tracheal extubation, postoperative antibiotics use, well glycemic control, SD of blood glucose and occurrence of complication. After excluding gestational age (with post-conceptual age) and gestational weight (with preoperative weight) because of collinearity, 12 factors were included in the subsequent multivariate logistic regression analysis. That analysis identified long duration of endotracheal intubation in NICU(OR = 1.239, 95%CI = 1.016–1.512, p = 0.035) and long days of antibiotics use(OR = 1.421, 95%CI = 1.233–1.637, p < 0.001) as risk factors for a prolonged postoperative hospital stay, whereas a high preoperative weight (OR = 0.995, 95%CI = 0.992–0.997, p < 0.001), well glycemic control(maintenance of perioperative blood glucose concentrations in the range of 47 to 150 mg/dL) (OR = 0.129, 95%CI = 0.031–0.535, p = 0.005) were identified as factors that protected against a prolonged postoperative hospital stay (Table 5).

Table 3
Association between preoperative variables and postoperative hospital stay.

	Total	Postoperative hospital stay ≤ 28days	Postoperative hospital stay > 28 days	P
Variable	**(n = 204)**	**(n = 130)**	**(n = 74)**	
Gender				0.119
Male	132(64.7%)	79(60.8%)	53(71.6%)	
Female	72(35.3%)	51(39.2%)	21(28.4%)	
Gestational age(weeks)	31.91 ± 2.63	32.54 ± 2.61	30.82 ± 2.30	< 0.001
Gestational weight(g)	1725.15 ± 550.03	1894.06 ± 586.17	1431.18 ± 309.37	< 0.001
Type of delivery				0.668
caesarean delivery	147(72.1%)	95(73.1%)	52(70.3%)	
natural labor	57(27.9%)	35(26.9%)	22(29.7%)	
Post-conceptual age (weeks)	36.01 ± 3.65	37.06 ± 3.64	34.16 ± 2.87	< 0.001
Preoperative weight (g)	2003.02 ± 510.05	2185.39 ± 504.43	1682.65 ± 332.44	< 0.001
Preoperative hemoglobin (g/l)	114.92 ± 24.11	113.35 ± 19.99	118.88 ± 26.83	0.125
Preoperative albumin (g/l)	29.46 ± 4.65	29.84 ± 4.67	28.79 ± 4.57	0.121
Preoperative creatinine (g/l)	47.85 ± 15.67	45.08 ± 13.76	52.70 ± 17.63	0.001
Preoperative CRP (mg/l)	29.9(6.70,78.83)	31.05(6.48,79.08)	29.35(7.11,77.70)	0.533
Preoperative SBP (mmhg)	65.36 ± 11.46	65.55 ± 11.33	65.03 ± 11.76	0.757
Preoperative DBP (mmhg)	35.06 ± 8.65	35.75 ± 8.32	33.85 ± 9.14	0.133
Preoperative HR (bmp)	146.35 ± 12.29	146.13 ± 12.34	146.74 ± 12.29	0.733
Preoperative inotrope drugs				0.154
Yes	39(19.1%)	21(16.2%)	18(24.3%)	
No	165(80.9%)	109(83.8%)	56(75.7%)	

	Total	Postoperative hospital stay ≤ 28days	Postoperative hospital stay > 28 days	P
GDR one day before surgery (mg/kg/min)	6.83 ± 0.96	6.88 ± 0.93	6.74 ± 1.02	0.317
GDR on the day of surgery (mg/kg/min)	6.59 ± 1.19	6.59 ± 1.27	6.59 ± 1.06	0.993

Table 4

Association between intra-and postoperative variables and postoperative hospital stay.

	Totally	Postoperative hospital stay ≤ 28days	Postoperative hospital stay > 28days	P
Variable	**(n = 98)**	**(n = 130)**	**(n = 74)**	
ASA classification				< 0.001
2 and 3	136(66.7%)	99(76.2%)	37(50%)	
4	68(33.3%)	31(23.8%)	37(50%)	
Entry into O.R. with endotracheal tube				< 0.001
Yes	80(39.2%)	38(29.2%)	42(56.8%)	
No	124(60.8%)	92(70.8%)	32(43.2%)	
Duration of surgery (min)	89.00 ± 26.87	89.89 ± 28.17	87.43 ± 24.52	0.531
Duration of anesthesia (min)	107.02 ± 29.37	109.18 ± 32.02	103.22 ± 23.75	0.163
Hemodynamic fluctuations				0.024
Yes	53(26%)	27(20.8%)	26(35.1%)	
No	151(74%)	103(79.2%)	48(64.9%)	
Blood loss (ml)	5 (5,10)	5 (2.75,10)	10 (5,10)	< 0.001
Fluid balance (ml)	20(18.5,40)	20(20,40)	20(15,40)	0.236
Perioperative blood transfusion(ml)	30(0,30)	30(0,30)	30(0,30)	0.987
Perioperative blood transfusion				0.178
Yes	134(65.7%)	81(62.3%)	53(71.6%)	
No	70(34.3%)	49(37.7%)	21(28.4%)	
Postoperative hemoglobin(g/l)	104.77 ± 14.43	105.77 ± 13.44	103.03 ± 15.97	0.193
Postoperative albumin (g/l)	35.05 ± 7.32	35.30 ± 6.79	34.60 ± 8.21	0.514
duration of extubation				

	Totally	Postoperative hospital stay ≤ 28days	Postoperative hospital stay > 28days	P
time at O.R.(min)	15(10,20)	15 (10,20)	12 (10,20)	0.861
time in ICU (days)	4 (3,7)	4(2,5)	7(4,12)	< 0.001
GDR one day after surgery(mg/kg/min)	7.06 ± 0.93	7.10 ± 0.96	7.00 ± 0.89	0.43
Antibiotic use (day)	18.47 ± 8.48	13.99 ± 4.41	26.34 ± 8.18	< 0.001
Occurrence of complications				< 0.001
Yes	84(41.2%)	32(24.6%)	52(70.3%)	
No	120(58.8%)	98(75.4%)	22(29.7%)	
Well glycemic control				< 0.001
Yes	111(54.4%)	88(67.7%)	23(31.1%)	
No	93(45.6%)	42(32.3%)	51(68.9%)	
Glucose value	105.29 ± 16.21	103.39 ± 15.84	108.63 ± 16.43	0.026
SD of BG	36.83 ± 10.20	34.88 ± 9.73	40.26 ± 10.17	< 0.001

Table 5
Risk factors for a prolonged postoperative hospital stay.

Parameters	Univariate Logistic model			Multivariate Logistic model		
	OR	95%CI	P	OR	95%CI	P
Large post-conceptual age (week)	0.693	0.602–0.796	< 0.001			0.489
High Preoperative weight(g)	0.996	0.995–0.997	< 0.001	0.995	0.992–0.997	< 0.001
High preoperative creatinine(g/l)	1.032	1.013–1.052	0.001			0.669
Entry into O.R. with endotracheal tube	3.178	1.752–5.763	< 0.001			0.784
High ASA classification	3.194	1.738–5.869	< 0.001			0.934
Hemodynamic fluctuations	2.066	1.091–3.912	0.026			0.568
Blood loss (ml)	1.099	1.036–1.166	0.002			0.16
Long duration of tracheal extubation (days)	1.272	1.137–1.424	< 0.001	1.239	1.016–1.512	0.035
Well glycemic control	0.215	0.116–0.398	< 0.001	0.129	0.031–0.535	0.005
High SD of BG	1.060	1.027–1.093	< 0.001			0.536
Long days of Antibiotics use (days)	1.436	1.294–1.593	< 0.001	1.421	1.233–1.637	< 0.001
Occurrence of complication	7.239	3.822–13.708	< 0.001			0.695

Discussion

Results of this retrospective study showed that among patients undergoing open abdominal surgery for NEC, maintaining perioperative blood glucose level in a range of 47 to 150 mg/dL was associated with a shorter postoperative hospital stay. Long duration of tracheal extubation in NICU, long days of antibiotics use and low gestational weight are risk factors for a prolonged postoperative hospital.

Long-term hypoglycemia can lead to profound adverse neurodevelopmental consequences, poor feeding and delays in growth and development, all of which can prolong a patient's postoperative hospital stay.[17] Duckrow [18]found that regional cerebral blood flow decreases during chronic and acute hyperglycemia

which can cause cerebral hypoxia and has been described as an important risk factor for production of neurologic damage[19]. A study by Hay[11] suggested that prolonged hyperglycemia might have a deleterious effect on lung development, perhaps by inducing hyperosmolarity or triggering oxidative stress. It is well established that the incidence of bronchopulmonary dysplasia increases with decreasing birth weight, and the resultant decreased growth rate and increased oxygen requirements lengthen an infant's postoperative hospital stay. We has already known that low gestational age is a risk factor for NEC progression.[20, 21]Another study found that newborns with a lower birth weight and an early stage of NEC were more likely to develop severe NEC. [22] Low perioperative weight is considered to be a type of immature development and to reflect a low adaptive response to stress caused by surgery and anesthesia. Entering into the operation room with endotracheal tube reflects respiratory failure before surgery and postoperative longer days of antibiotics use means severe infection and therefore obviously prolonged neonates' hospitalization. Our findings in the present study are consistent with those in previous studies. Hence, perioperative glycemic control, preoperative weight, Enter into the operation with endotracheal tube and antibiotics use all have impact on postoperative hospital stay, and also the prognosis of neonates with NEC.

In our study, perioperative glucose monitoring showed that episodes of intraoperative low glucose concentration were more common in poor glycemic control group, whose preoperative glucose delivery rate were lower than that in well glycemic control group though not significant (6.79 ± 1.17 mg/kg/min vs 7.11 ± 1.55 mg/kg/min, $p > 0.05$). And some of them occurred persistent hyperglycemia during post-operative period(24 hours after surgery). This finding may possibly be due to a decreased responsiveness of β-cells in premature pancreas of preterm neonates. Under stress, derangements in glucose homeostasis may lead to hyperglycemia when glucose infusions exceeding their normal glucose turnover rate due to an immature response to pathoglycemia. Because no standard transfusion protocol was used, our hospital used either 1% or 5% glucose-containing solution or normal saline through the infusion pump to maintain fluid and glucose homeostasis during surgery. However, the hypoglycemia could not be rapidly or excessively corrected, because a rapid correction of hypoglycemia has been reported to be associated with a poor outcome. Studies in an animal model have also demonstrated that higher blood glucose concentrations during recovery from hypoglycemia can worsen neurologic damage, at least in part because of an increased generation of reactive oxygen species.[23, 24] Perioperative glycemic fluctuations were more common in poor glycemic control group (SD of blood glucose: 43.78 ± 7.91 mg/dL vs 31.01 ± 8.05 mg/dL, $p < 0.001$). Patients whose postoperative hospital stay longer than 28 days after had higher SD of blood glucose levels than control (40.26 ± 10.17 mg/dL vs 34.88 ± 9.73 mg/dL, $p < 0.001$). Glycemic fluctuation can increase the serum levels of chronic inflammatory marker (high-sensitivity C-reactive protein) and lead to an overproduction of free radicals then inducing oxidative stress.[25] Fluctuation of blood glucose levels increased hospital stay via influencing wound healing and infection. A large meta analysis looking at over 4000 patients from six studies showed that tight glycemic control does not improve mortality or outcome other than dialysis needs in pediatric intensive care units. The main difference of our study is that our study focused on perioperative period. Perioperative hyperglycemia might be considered as a marker of high stress level. And due to the derangements in glucose homeostasis in critical ill neonates, many of them occurred hyperglycemia after treatment of hypoglycemia. Evans believed that hyperglycemia in the perioperative period is associated with increased morbidity, decreased survival, and increased resource

utilization[26]. Our study is consistent with that. Trying to avoid perioperative hypoglycemia, hyperglycemia and glucose variability may help to optimize patients' outcome around NEC surgery. It's not contradictory to the previous study which demonstrated that tight glucose control does not result in a decrease in hospital mortality in pediatric intensive care units[27].

Perioperative abundant nutrition is beneficial to attenuate stress response which improve surgical outcome. Low glycogen storage rate, impaired gluconeogenesis and ketogenesis in neonates make them more likely to suffer from hypoglycemia. Carbohydrate loading is necessary to meet the increased energy demands of stressed patients. Several studies focused on perioperative glucose-containing solution. European guideline suggested intraoperative 1-2.5% balanced glucose-containing solution is safe to prevent hypoglycemia and hyperglycemia, but need careful monitoring and management.[28] Our study found that pathoglycemia and glycemic variability were common in critically ill neonates and decreasing glucose fluctuation during hospitalization for surgery is important. Little information is available to guide clinicians in how glycemic variability can be reduced but careful glucose monitoring and management may help. Due to deranged glucose homeostasis of neonates and the painful nature of capillary or venous blood testing, noninvasive continuous glucose monitoring may be a good strategy for favourable perioperative blood glucose control. Additional randomized trials are needed to settle the debate about what constitutes a normal neonatal glucose value and the best method of perioperative glucose infusion. Furthermore, new methods for the careful monitoring and control of perioperative glucose levels need to be developed. No definite threshold exists for a normal neonatal blood glucose concentration, mainly because of a lack of data concerning the impact of blood glucose concentrations on the short- and long-term clinical outcomes of neonates.

Our study has several limitations that should be mentioned. Its main limitation is the potential for bias in the inclusion/exclusion criteria due to the study's retrospective design. Glucose derangements might be a marker of severity of illness, which prejudge the outcome, although there is no statistical significance in gestational age, gestational weight, preoperative CRP and ASA between two groups. Second, although a blood glucose concentration of 47 mg/dL is well-accepted as the threshold for treating hypoglycemia in newborns, there is no evidence that intervention at that threshold is safe or effective.[29] However, McKinlay[30] found in his prospective study that treatment of neonatal hypoglycemia starting at a threshold of 47 mg of glucose per deciliter was not associated with any subsequent adverse neurodevelopmental outcomes at 2 years. At present, there is no reliable tool that can be used to assess the neurologic state related to a blood glucose concentration in infants. Therefore, clinicians need a pragmatic threshold that indicates when to provide treatment needed to ensure an adequate supply of metabolic fuel for the developing brain during the neonatal transition period. Meanwhile, adverse outcomes have been reported at blood glucose levels > 150 mg/dL, and the threshold for significant neonatal hyperglycemia remains unclear. In this study, we regarded a perioperative glucose concentration in the range of 47 to 150 mg/dL as well glycemic control; however, that definition may not be sufficiently precise. Third, the intervals and frequency of blood glucose tests (24 hours before, during and 24 hours after surgery) were not the same for each patient, although each patient was measured for blood glucose at least five times in total. A few patients may have been mistakenly allocated to the well glycemic control group because an abnormal glucose value was not detected in time due to observation bias. Arterial punctures for blood gas analysis are difficult to perform in

all infants in China (similar to any developing country) during surgery. Therefore, various biochemical parameters, such as electrolyte levels, were not included in our analysis because the data were unavailable. We didn't include patients under 28 weeks because few infants delivered at this gestational age range underwent NEC surgery in our hospital and meanwhile these few infants may cause obvious bias to the LOS due to their extremely immature development. In addition to the retrospective nature of our study, other limitations also exist. As a single-center study, our results should not be extrapolated to patients treated at other centers.

Nevertheless, our results showed that perioperative blood glucose control is necessary for the optimal treatment of neonatal NEC, and has a positive impact on the patient's postoperative hospital stay and overall prognosis. This study was undertaken to gain a better understanding of glucose monitoring and control in the perioperative period and to broaden the understanding of how hypoglycemia and hyperglycemia, as well as glucose variability, are associated with hospital length of stay in critical ill population. However, these observational findings require further verification in randomized clinical trials.

Conclusions

Perioperative glucose levels outside of a prespecified range were an independent risk factor for a prolonged hospital stay in a population of neonates undergoing surgical repair for NEC. Careful perioperative blood glucose monitoring and control may be crucial for achieving better outcomes for neonates with NEC.

List Of Abbreviations

NEC: Necrotizing Enterocolitis; LOS: Length of Stay; IRB: Institutional Review Board; O.R.: Operation Room; GDR: Glucose Delivery Rate; CRP: C-reactive Protein; ASA: American Society of Anesthesiologists; OR: Odds Ratio; SD: Standard Deviation; NICU: Neonatal Intensive Care Unit.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Clinical Research Ethics Committee of China Medical University, Shengjing Hospital (2018PS515K). The initial IRB approval is dated November 22, 2018. Due to the retrospective nature of this study, and the fact that all pertinent data had been obtained from patient medical records, the local Ethics Committee agreed that the study did not require written informed consents.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

All authors made substantial contributions to the study and met the criteria for authorship defined in the author instructions: NG contributed to acquisition, analysis and interpretation of data, and drafting of the manuscript; HJ contributed to acquisition and analysis of data; DT contributed to the collection of data; JY contributed to the collection of data. PZ: supervised the project, analyzed data and wrote manuscript. All authors participated manuscript preparation and approved the final manuscript.

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Figures

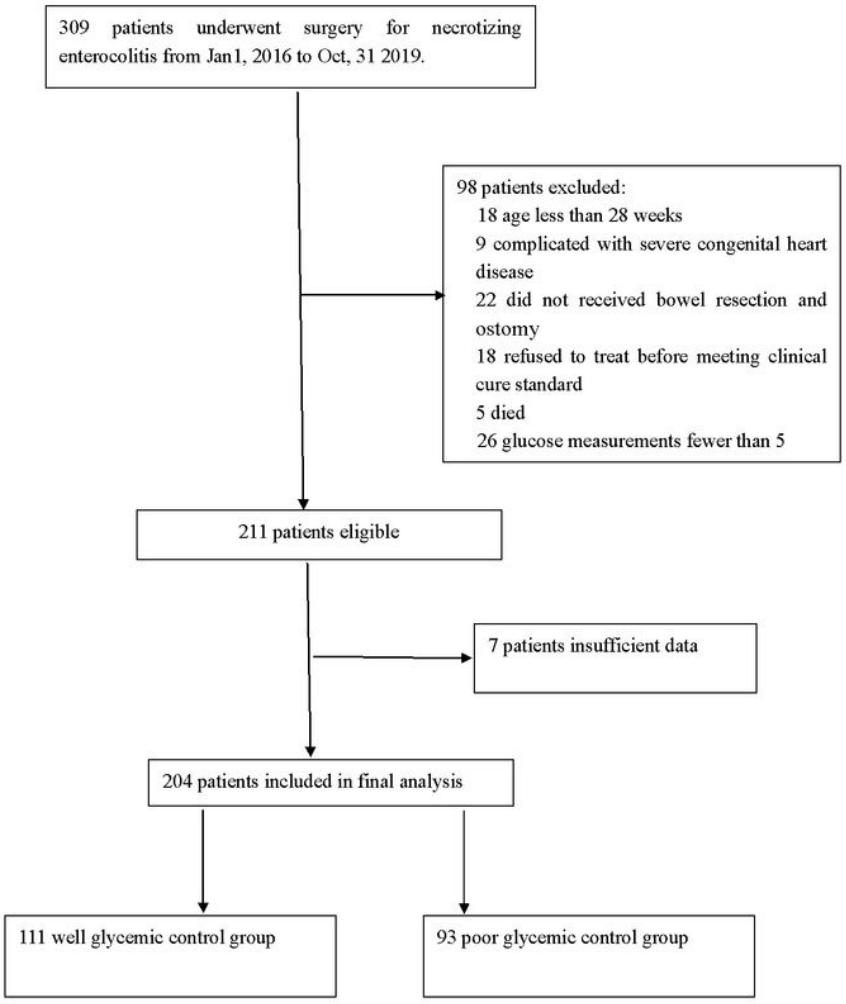

Figure 1

Flowchart of the study