Impact of Enteral Feeding on Cerebral and Splanchnic Oxygenation During Packed Red Blood Cell Transfusion in Preterm Infants: A Randomised Controlled Trial

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ABSTRACT

Objective: To investigate the impact of enteral feeding during packed red blood cell transfusion (PRBCT) on splanchnic and cerebral regional oxygenation ($sRSO_2$, $cRSO_2$) in very-low-birthweight (VLBW) neonates.

Study Design: Randomised controlled study.

Place and Duration of the Study: Department of Neonatology, Faculty of Medicine, Akdeniz University, Antalya, Turkiye, from June 2021 to June 2024.

Methodology: Fifty-six VLBW neonates were categorised into No-feeding and Feeding groups. $sRSO_2$, $cRSO_2$, the ratio of $sRSO_2$ to $cRSO_2$ (SCOR), splanchnic and cerebral fractionated tissue oxygen extraction (sFTOE, cFTOE) were measured at predetermined intervals using near-infrared spectroscopy. Bonferroni-corrected linear mixed models were used to assess repeatedly measured variables across different time points.

Results: An overall increase in $sRSO_2$ and $cRSO_2$ was observed during the study. In contrast to a steady $sRSO_2$ incline in the No-feeding group, the Feeding group exhibited a temporary reduction in $sRSO_2$ and SCOR, followed by an increase in sFTOE during the first hour of PRBCT (ΔMean = −1.958, ΔMean = −0.024, ΔMean = 2.088, respectively). Despite the changing patterns in splanchnic oxygenation, the mean differences in $sRSO_2$ and sFTOE between the two groups were −0.67 (95% CI: −2.74 – 1.40, p = 0.520) and 0.83 (95% CI: −1.46 –3.12, p = 0.473), indicating the impact of enteral feeding on $sRSO_2$ was insignificant.

Conclusion: The findings demonstrated improved outcomes in both cerebral and splanchnic oxygenation during PRBCT in stable preterm infants, despite a temporary impairment in splanchnic tissue oxygen utilisation in the Feeding group. Enteral feeding alone did not pose a risk for transfusion-associated necrotising enterocolitis (TANEC). Large-scale studies are warranted to clarify the complex interplay between enteral feeding, transfusion, and tissue oxygenation.

Key Words: *Blood transfusion, Enteral feeding, Preterm infants, Very-low-birthweight infants, Splanchnic regional oxygenation, Cerebral regional oxygenation, Transfusion-associated necrotising enterocolitis.*

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INTRODUCTION

Anaemia of prematurity is a common complication in preterm neonates in neonatal intensive care units (NICUs), necessitating frequent packed red blood cell transfusions (PRBCT) to increase oxygen delivery to vital organs.[1] However, trans- fusion itself carries inherent risks. Transfusion-associated necrotising enterocolitis (TANEC) refers to the development of necrotising enterocolitis (NEC), with significant morbidity and mortality, within 48–72 hours after transfusion. Although the aetiology remains a topic of ongoing debate, proposed mechanisms linking PRBCT to TANEC include anaemia, previous transfusions, transfusion of blood after prolonged storage, and enteral feeding.[1] Anaemia causes hypoxia in the gastrointestinal (GI) tract, while PRBCT leads to intestinal tissue reperfusion and oxidative stress, thereby triggering an inflammatory cascade.[1,2]

Enteral feeding during PRBCT adds another layer of complexity to the pathophysiology of TANEC. Theoretically, feeding increases splanchnic blood flow; however, paradoxically, PRBCT has been associated with significant decreases in postprandial splanchnic regional oxygenation ($sRSO_2$), potentially contributing to reperfusion injury in the immature GI tract of preterm infants.[3,4] Despite this, the role of enteral feeding in TANEC remains controversial. Some studies have suggested that withholding enteral feeding may reduce the risk of TANEC,[5,6] while others reported that continuing, withholding, or restricting feeding did not appear to be associated with differ-

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ences in $sRSO_2$.[3,7,8] As a result, the impact of enteral feeding on $sRSO_2$ remains unclear, partly due to heterogeneous patient populations that limit generalisability and reduce the statistical power needed to adjust for TANEC confounders. These inconsistencies have led to significant variations in nutritional practices across NICUs.[1] In this context, a randomised controlled trial (RCT) using near-infrared spectroscopy (NIRS) — a non-invasive, real-time technique used to assess tissue oxygenation in very-low-birthweight (VLBW) neonates — was conducted to investigate the impact of enteral feeding during PRBCT on $sRSO_2$ and regional oxygenation ($cRSO_2$).

METHODOLOGY

This single-centre, prospective randomised controlled trial was approved by the Akdeniz University's Ethical Committee for Clinical Studies (Approval No. KAEK-737; Dated: 23.09. 2020) and was registered on ClinicalTrials.gov (Identification No. NCT06632314). The study adhered to the Declaration of Helsinki and followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Written informed consent was obtained from the legal guardians of all infants.

The study enrolled neonates born at ≤32 weeks of gestation and/or with a birth weight ≤1500 grams who were admitted to the NICU and received PRBCT between June 2021 and 2024. Inclusion criteria were haemodynamically stable VLBW neonates receiving PRBCT who tolerated a minimum total daily feeding volume of 100 mL/kg/day and had survived at least the first week of life. Infants were excluded if they met any of the following criteria: feeding intolerance,[9] stage II or higher NEC,[10] spontaneous intestinal perforation,[10] abdominal surgery, suspected or proven sepsis within the preceding 72 hours, requirement for high-frequency oscillatory ventilation previous PRBCT (to avoid sensitisation to blood products), haemodynamically significant patent ductus arteriosus diagnosed by a paediatric cardiologist, complex congenital anomalies involving the GI tract or cardiovascular system, missing data, or refusal to provide consent.

A priori analysis using G*Power software version 3.1.9.4 estimated that a sample size of 54 neonates would achieve 80% power with a type I error rate of 5% to detect an unadjusted difference between the groups. To account for potential missing data, 56 infants were randomised. Using a non-stratified web-based randomisation technique, participants were divided into two groups in a 1:1 ratio: the No-feeding group (n = 29), in which feedings were withheld for 1 hour before and 2 hours after PRBCT, and the Feeding group (n = 27). Randomisation was performed through sequentially numbered, sealed, opaque envelopes. Blinding was not possible due to the open assignment of feeding regimens to families, clinical staff, and researchers. Perinatal data and clinical characteristics of the infants were recorded.

In accordance with institutional policy, breast milk *via* orogastric tubes was the first choice for enteral feeding in VLBW infants. Intermittent bolus trophic feeding was initiated at 20 mL/kg/day every 2 hours, unless clinically contraindicated. If well-tolerated, the feeding volume was increased by 20–30 mL/kg/day. To deliver 3.5–4 g/kg/day of protein for catch-up growth, breast milk was fortified—two scales of fortifiers were added to 50 mL, once enteral feeding reached 80 mL/kg/ day—and continued, until the infant reached 2000 - grams or was discharged. If breast milk was unavailable or insufficient (the institution does not operate a milk bank), undiluted preterm formula was administered.

Enteral feeding was maintained in the Feeding group per the institution's protocol, while the No-feeding group received an intravenous mixed dextrose/saline solution during the feeding restriction period.

The decision to transfuse PRBCT at a dose of 15–20 mL/kg over 4 hours was made by the attending neonatologist according to the criteria outlined in the transfusion guidelines (Appendix 1).[2,11] The centre's policy requires ABO- and Rh-compatible, leukocyte-reduced, and irradiated red blood cells in paediatric transfusion bags with a haematocrit of 50–55%. Each PRBCT was considered a separate event; no infant received more than one transfusion during the study.

Two NIRS probes (INVOS™ 5100C Reusable Sensor Cable Channel-4) were placed on the central region of the forehead and the lower quadrant of the abdomen, just below the umbilicus, and secured with elastic tape. $cRSO_2$ and $sRSO_2$ were measured using an INVOS™ 5100C cerebral/somatic oximeter (Medtronic, Minneapolis, MN, USA) at predetermined intervals: immediately before PRBCT (baseline) and at 1, 6, 12, 24, and 48 hours. A baseline period of 10–15 minutes was allowed for stabilisation and excluded from analysis, with average measurements recorded after at least 10 minutes of consecutive data. Artefacts were defined as physiologically inexplicable changes in $cRSO_2$ or $sRSO_2$ (*e.g.*, a 30% change between two subsequent data points),[12] or missing values due to probe misplacement (*i.e.*, absence of physiological variability). The ratio of splanchnic-to-cerebral regional oxygenation (SCOR) and fractionated tissue oxygen extraction (FTOE) was calculated, using the formula $[(SpO_2 - rSO_2)/SpO_2] \times 100$, where SpO_2 represents pulse oxygen saturation and rSO_2 represents regional tissue oxygen saturation, thereby reflecting tissue oxygen extraction. An increase in FTOE indicated inefficient tissue oxygen utilisation.[13] Additionally, vital signs, including oxygen saturation, were measured at 30-minute intervals using the Nellcor™ Bedside SpO_2 Patient Monitoring System (Covidien Ireland Limited, Tullamore, Ireland). Infants received oxygen to maintain a target SpO_2 range of 90-95%, regardless of whether they were breathing independently or receiving ventilation support.

Statistical analysis was performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA), with images generated using MedCalc Statistical Software version 22 (free trial). The Chi-square or Fisher's exact tests were used for categorical variables, while the independent samples t-tests or the Mann-Whitney U tests were used for numerical variables, following normality assumptions. Repeated-measures ANOVA was used

to assess the differences within the groups across time points, with Mauchly's test and Greenhouse-Geisser corrections applied for sphericity violations, followed by pairwise comparisons using Bonferroni-adjusted paired-samples t-test on estimated marginal means. A mixed ANOVA was employed to evaluate the changes over time between the groups (time x group interactions). For repeated variables not meeting normality assumptions, the Friedman test was applied, followed by Wilcoxon signed-rank tests for pairwise comparisons of dependent variables.

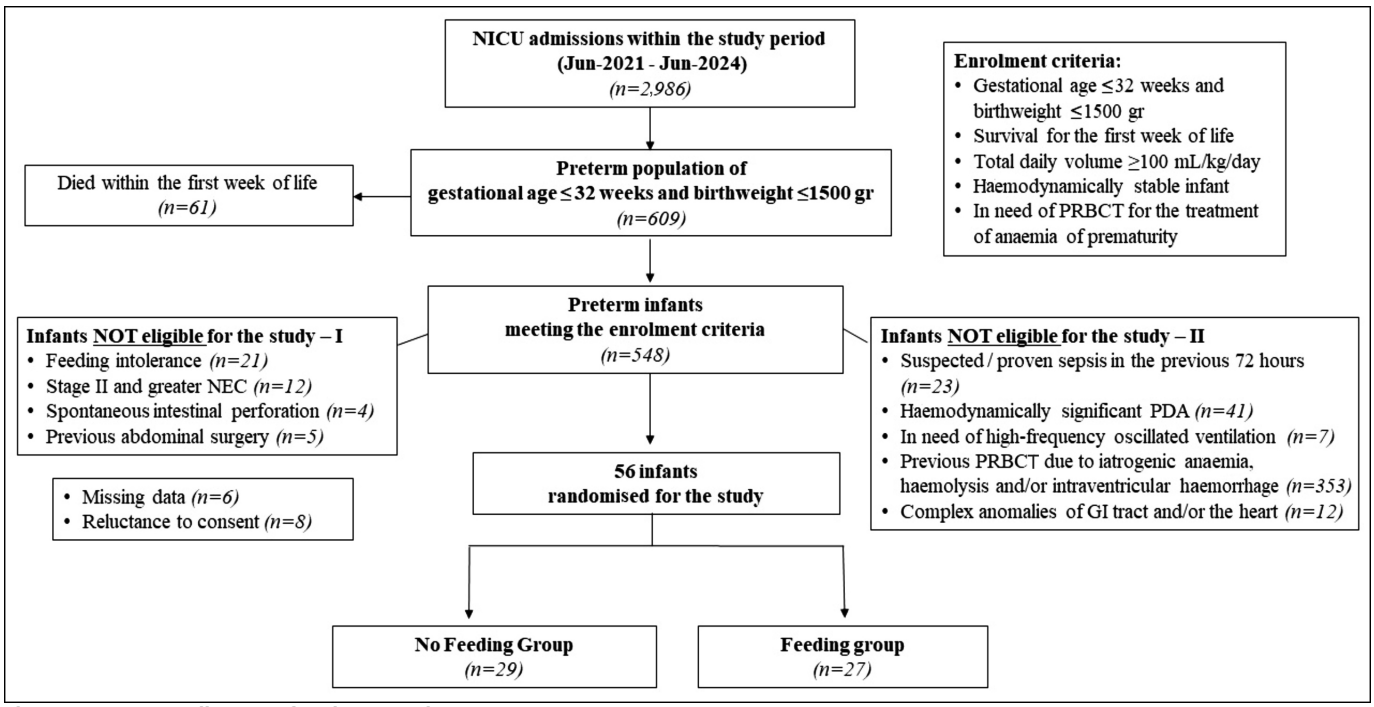


Figure 1: CONSORT diagram of patient recruitment.

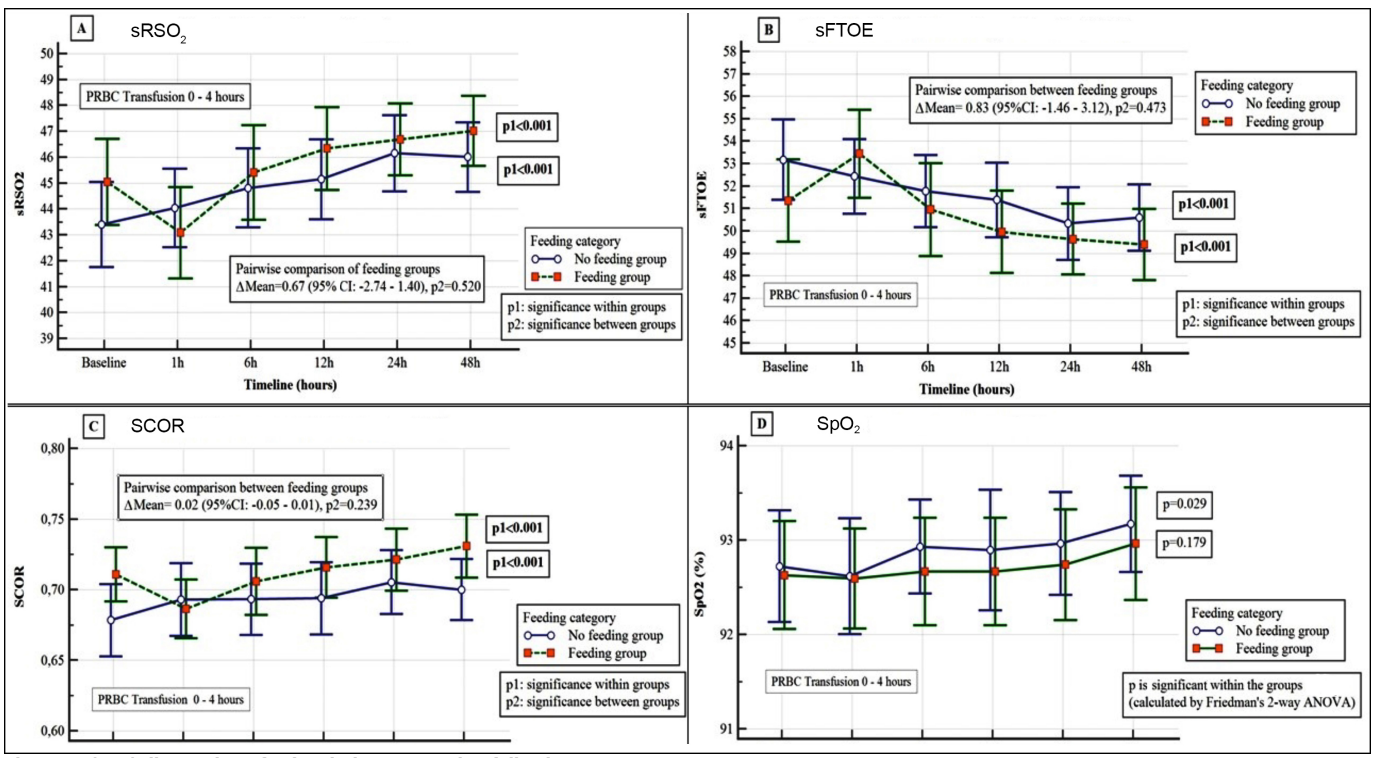


Figure 2: (A-D) Illustration of splanchnic oxygenation following PRBCT.

Table I: Demographic and clinical features of the preterm neonates.

Variables, n (%)	No-feeding group (n = 29)	Feeding group (n = 27)	p-values
Maternal age (years)*	29 (6)	32 (8)	**0.011**
Gestational age (week)*	29 (3)	29 (4)	0.960
Birthweight (gr)**	1015.52 ± 212.01	1000.19 ± 204.92	0.785
Gender – Females***	16 (55.2%)	16 (59.3%)	0.757
C/S delivery***	26 (89.7%)	20 (74.1%)	0.171
Twin birth***	6 (20.7%)	5 (18.5%)	0.838
5-min Apgar <7***	3 (10.3%)	2 (7.4%)	>0.990
Antenatal steroids***	16 (55.2%)	11 (40.7%)	0.280
Chorioamnionitis***	6 (20.7%)	2 (7.4%)	0.254
SGA***	1 (3.4%)	4 (14.8%)	0.185
Respiration support* **			
Spontaneous breathing	7 (24.1%)	3 (11.1%)	0.529
Low-flow oxygen	9 (31.0%)	8 (29.6%)	
Non-invasive ventilation†	10 (34.5%)	16 (59.3%)	
Invasive ventilation	3 (10.3%)	-	
PRBCT			
Day of life at the time of the study, (day)*	13 (2.5)	14 (2)	0.192
Actual weight, (gr)**	1158.28 ± 231.72	1142.22 ± 203.15	0.785
Pre-transfusion Hb (g/dL)*	8.3 (0.9)	8.1 (0.5)	0.526
Post-transfusion Hb (g/dL)*	10.9 (0.6)	10.8 (1.3)	0.490
Enteral feeding			
Day of first enteral feeding (day)*	2 (1)	2 (2)	0.153
Daily feeding intake (ml/kg/day)*	146 (9.5)	140 (18)	0.895
Source of enteral feeding***			
Maternal milk ± fortifier	16 (55.2%)	16 (59.3%)	
Maternal milk ± preterm formula	7 (24.1%)	8 (29.6%)	0.598
Preterm formula	6 (20.7%)	3 (11.1%)	

Values with median (interquartile range), and p-values are tested using the Mann-Whitney U test; ** Values expressed as mean ± standard deviation, and p-values are tested using the Student t-test. * Chi-square or Fisher's exact tests assessed the statistical difference of categorical variables. † Non-invasive ventilation in the form of CPAP and/or NIPPV therapy. C/S delivery: Caesarean section; SGA: Small for gestational age; PRBCT: Packed red blood cell transfusion; Hb: Haemoglobin.*

Table II: Descriptive values of oxygenation indices.

Variables	No-feeding Group	Feeding Group	p-values
$sRSO_2$ (%)			
Baseline	43.40 ± 4.34)	45.04 ± 4.21	0.157
1st hour	44.04 ± 3.98	43.09 ± 4.45	0.401
6th hour	44.81 ± 4.01	45.41 ± 4.61	0.605
12th hour	45.14 ± 4.06	46.33 ± 4.02	0.277
24th hour	46.15 ± 3.87	46.68 ± 3.51	0.594
48th hour	46.01 ± 3.52	47.01 ± 3.42	0.285
$cRSO_2$ (%)			
Baseline	65.30 (3.41)	64.24 (4.79)	0.345*
1st hour	64.63 (4.17)	62.86 (2.96)	0.151*
6th hour	65.52 (3.39)	63.98 (2.55)	0.354*
12th hour	65.30 (6.20)	64.73 (5.88)	0.450*
24th hour	65.58 ± 4.46	64.83 ±3.80	0.503
48th hour	65.85 ± 3.65	64.45 ± 3.82	0.129
SpO_2 (%)			
Baseline	92.72 ± 1.55	92.63 ± 1.45	0.815
1st hour	93.00 (3.00)	92.00 (3.00)	0.953*
6th hour	93.00 (2.00)	92.00 (2.00)	0.438*
12th hour	93.00 (3.00)	92.00 (3.00)	0.597*
24th hour	93.00 (2.00)	93.00 (2.00)	0.650*
48th hour	93.00 (2.00)	93.00 (3.00)	0.573*
SCOR			
Baseline	0.68 ± 0.07	0.71 ± 0.04	**0.041**
1st hour	0.69 ± 0.07	0.69 ± 0.05	0.688
6th hour	0.69 ± 0.07	0.71 ± 0.06	0.461
12th hour	0.69 ±0.07	0.72 ± 0.05	0.191
24th hour	0.71 ± 0.06	0.72 ± 0.06	0.304
48th hour	0.70 ± 0.06	0.73 ± 0.06	**0.046**
sFTOE (%)			
Baseline	53.17 ± 4.71	51.36 ± 4.64	0.151
1st hour	52.43 ± 4.38	53.45 ± 4.97	0.423
6th hour	51.77 ± 4.23	50.95 ± 5.24	0.523
12th hour	51.39 ± 4.37	49.96 ± 4.61	0.241
24th hour	50.33 ± 4.25	49.64 ± 3.97	0.529
48th hour	50.59 ± 3.91	49.34 ± 4.00	0.260
cFTOE (%)			
Baseline	30.67 (4.39)	30.92 (6.76)	0.549*
1st hour	30.49 (3.45)	32.01 (5.04)	0.210*
6th hour	30.26 ± 3.98	30.54 ± 4.31	0.806
12th hour	26.64 ± 4.27	30.04 ± 4.58	0.827
24th hour	29.78 ± 4.97	30.08 ± 4.14	0.235
48th hour	29.31 ± 3.96	30.63 ± 4.33	0.235

*Variables meeting the normality assumption are expressed as mean ± standard deviation, and p-values are derived from the Student's t-test. * Symbol denotes variables not meeting the normality assumption that are expressed as median (IQR), and p-values are calculated by the Mann-Whitney U test, indicating the statistically significant differences between the two groups at specific time points. $cRSO_2$: Cerebral regional oxygen saturation; $sRSO_2$: Splanchnic regional oxygen saturation; SpO_2: Pulse oxygen saturation; SCOR: The ratio of splanchnic-to-cerebral oxygenation; cFTOE: Cerebral fractional tissue oxygen extraction; sFTOE: Splanchnic fractional tissue oxygen extraction.*

Table III: The distribution of the changes in oxygenation indices

Variables	Timeline		No-feeding Group		Feeding Group	
			Mean difference	P2	Mean difference	P2
$sRSO_2$	Baseline	1st hour	0.639	0.055	-1.958	**<0.001**
		6th hour	1.417	**<0.001**	0.373	>0.999
		12th hour	1.747	**<0.001**	1.292	**0.016**
		24th hour	2.753	**<0.001**	1.641	**0.027**
		48th hour	2.612	**<0.001**	1.973	**0.027**
	P1			**<0.001**		**<0.001**
sFTOE	Baseline	1st hour	-0.746	0.060	2.088	**<0.001**
		6th hour	-1.408	**<0.001**	-0.402	>0.99
		12th hour	-1.789	**<0.001**	-1.392	**0.012**
		24th hour	-2.840	**<0.001**	-1.716	**0.031**
		48th hour	-2.581	**<0.001**	1.963	0.051
	P1			**<0.001**		**<0.001**
SCOR	Baseline	1st hour	0.015	**0.001**	-0.024	**<0.001**
		6th hour	0.015	**0.001**	-0.005	>0.999
		12th hour	0.016	0.111	0.005	>0.999
		24th hour	0.027	**0.001**	0.010	>0.999
		48th hour	0.022	**0.004**	0.020	0.449
	P1			**<0.001**		**<0.001**
$cRSO_2$€	Baseline	1st hour	-1.071	0.284	-1.874	0.061**
		6th hour	2.866	**0.004**	3.004	**0.003****
		12th hour	4.142	**<0.001**	3.845	**<0.001****
		24th hour	3.947	**<0.001**	3.701	**<0.001****
		48th hour	4.640	**<0.001**	3.653	**<0.001****
	P1*			**<0.001***		**<0.001***
cFTOE€	Baseline	1st hour	-0.833	0.405	-1.658	0.097**
		6th hour	1.935	0.053	2.643	**0.008****
		12th hour	3.665	**<0.001**	3.676	**<0.001****
		24th hour	3.320	**0.001**	3.196	**0.001****
		48th hour	4.271	**<0.001**	2.835	**0.005****
	P1*			**<0.001***		**<0.001***
SpO_2€	Baseline	1st hour	-0.626	0.532	-0.243	0.808**
		6th hour	1.264	0.206	0.229	0.819**
		12th hour	0.927	0.354	0.277	0.782**
		24th hour	1.334	0.182	0.737	0.461**
		48th hour	2.696	**0.007**	1.856	0.063**
	P1*			**0.029***		0.179*

Repeated-measures ANOVA was employed to test the statistical significance of variables within the groups (P1). The Bonferroni-adjusted paired-samples t-test was used to assess the pairwise comparison at a specific time point (P2). € Symbol denotes variables not meeting the normality assumption, and Friedman's two-way analysis of variance was used to test the differences within the groups, presented by P1. The Wilcoxon signed-rank test was used to assess the pairwise comparison of non-normally distributed variables at specific time points, presented by P2**. $cRSO_2$: Cerebral regional oxygen saturation; $sRSO_2$: Splanchnic regional oxygen saturation; SpO_2: Pulse oxygen saturation; SCOR: The ratio of splanchnic-to-cerebral oxygenation; cFTOE: Cerebral fractional tissue oxygen extraction; sFTOE: Splanchnic fractional tissue oxygen extraction.*

Values were expressed as mean ± standard deviation or as median with interquartile range (IQR). A p-value of ≤0.05 was considered statistically significant.

RESULTS

In total, 56 VLBW neonates were enrolled in the study, with a median gestational age of 29 (IQR: 3) weeks and a birth weight of 1008.13 ± 206.86 grams. Figure 1 shows the CONSORT diagram for patient recruitment.

Perinatal characteristics and NIRS measurements for both groups are presented in Table I and II. Neonates in the No-feeding group had higher actual median weight, although the difference was not statistically significant when compared to the Feeding group (p = 0.785). There were no significant differences in the infants' characteristics, including pre- and post-transfusion haemoglobin values (p >0.05).

The changes in oxygenation indices within the groups are detailed in Table III and Figure 2. An overall increase in both $sRSO_2$ and $cRSO_2$ was observed over the 48-hour period of PRBCT (both p <0.001), while SpO_2 values remained relatively stable (p = 0.179 and = 0.029 in the Feeding and No-feeding groups, respectively). The pattern of change in $sRSO_2$ values differed significantly between the two groups. Infants in the No-feeding group demonstrated a steady increase in $sRSO_2$, while those in the Feeding group exhibited a decline in $sRSO_2$ values by the beginning of PRBCT (ΔMean = 0.639, p = 0.055 *vs.* ΔMean = −1.958, p <0.001).

In response to $sRSO_2$ deterioration in the Feeding group, a reduction in SCOR accompanied by an increase in splanchnic FTOE (sFTOE) was noted, suggesting impaired tissue oxygen utilisation within the splanchnic region (ΔMean = −0.024, p <0.001; ΔMean = 2.088, p <0.001, respectively).

Despite these changes in splanchnic oxygenation patterns, the mean differences in $sRSO_2$ and sFTOE between the two groups were −0.67 (95% CI: −2.74–1.40; p = 0.520) and 0.83 (95% CI: −1.46–3.12; p = 0.473), respectively, indicating that the impact of enteral feeding on these indices was not

significant (Figure 2). No infants experienced feeding intolerance or TANEC during the study period.

DISCUSSION

This study investigated the effects of enteral feeding during PRCBT at various time points, providing insights into the temporal interactions that influence key physiological parameters in haemodynamically stable VLBW preterm neonates. The intestines of term neonates mature rapidly and increase in weight up to tenfold within the first days of life.[14] Such rapid growth demands substantial oxygen. However, preterm neonates exhibit impaired oxygenation, immature blood flow autoregulation, and limited reserves for increased oxygen extraction. Consequently, local tissues may become hypoxic, potentially leading to TANEC.[6] Hypoperfusion and reperfusion injury, coupled with an inflammatory cascade and GI microbiota imbalance, trigger the underlying pathophysiological mechanisms.[1,3,8,15,16]

Blood transfusions in anaemic conditions, along with enteral feeding, are thought to precipitate TANEC,[1-4,16] yet debate continues as to whether to continue or withhold enteral feeding during transfusion. Under normal conditions, enteral feeding promotes intestinal motility, increases mesenteric blood flow, and enhances oxygen delivery *via* the release of local GI hormones. This typically results in improved splanchnic oxygenation and SCOR in non-anaemic, stable preterm neonates.[17] In contrast, in anaemic neonates, the expected postprandial oxygenation increase is not observed, leading to impaired oxygen utilisation in the splanchnic tissue.[12,17–19] When oxygen demands are not met, the intestinal barrier may be compromised, circulation reduced, and postprandial splanchnic oxygenation impaired, resulting in worsened FTOE.[12,17,20] Although some meta-analyses have recommended withholding feeding to avoid TANEC,[21] RCTs do not provide sufficient evidence to support delaying feeding to reduce NEC.[1,3,5,7,8,15] Data indicate that enteral feeding during transfusion can increase splanchnic oxygenation.[3,8] The findings of this study demonstrated improved outcomes in both splanchnic and cerebral oxygenation, with the decision to continue or withhold enteral feeding during PRBCT having no significant effect on splanchnic oxygenation in the preterm population. Infants who continued feeding experienced reduced $sRSO_2$ and SCOR, along with increased sFTOE during the first hour of PRBCT, whereas a steady rise in oxygenation was seen in the No-feeding group. The SCOR reflects changes in mesenteric oxygenation when cerebral autoregulation is intact,[2,7] and a SCOR below 0.75, combined with a $sRSO_2$ below 56%, has been associated with gut ischaemia and NEC.[19] These results imply that feeding infants may experience a temporary impairment in oxygen utilisation, likely due to increased oxygen consumption or a diminished oxygen-carrying capacity in the splanchnic tissue. However, once splanchnic autoregulation is established, oxygenation improves without any signs of GI discomfort, implying that enteral feeding alone does not pose a risk for TANEC despite the transient impairment. Further research is needed to explore the complex intertwining between enteral feeding and TANEC in unstable preterm neonates, particularly regarding confounding factors such as the type of food (formula versus breast milk) and elements of GI immaturity, including Caesarean section birth and limited use of antenatal steroids.

Neonatal cerebral circulation exhibits some degree of autoregulation, which generally protects cerebral oxygenation.[8] However, intestinal inflammation may lead to reduced $cRSO_2$ at the onset of NEC.[22] Previous studies have shown that a $cRSO_2$ below 71% in the first 8 hours after GI symptoms can predict complicated NEC with a specificity of 80%.[23] Given the hypothesis that PRBCT may induce NEC and affect neurodevelopmental outcomes, this study also evaluated the impact of transfusion on cerebral oxygenation. At the initiation of transfusion, a transient reduction in SpO_2 and $cRSO_2$, accompanied by an increase in cerebral FTOE, was noted irrespective of feeding status. This implies that the transfusion itself, rather than the decision to continue or withhold enteral feeding, led to a temporary impairment in cerebral oxygen utilisation due to increased consumption. Subsequent normalisation and even an increase in $cRSO_2$ indicated that cerebral autoregulation eventually adapted to meet oxygen demands. These observations align with a secondary analysis of the TOP-NIRS trial, which reported increased $cRSO_2$ and $sRSO_2$ following PRBCT, despite unchanged SpO_2 in VLBW infants.[24] Monitoring regional perfusion using NIRS in the cerebral tissue may be particularly useful when PRBCT is necessary in critically ill preterm neonates with compromised haemodynamic.

This RCT examined the impact of enteral feeding on $sRSO_2$ and $cRSO_2$ in the context of transfusion. However, several limitations should be noted. Blinding was not feasible due to the open assignment of feeding regimens, potentially introducing bias. The relatively small sample size limited the generalisability of the findings. With 50–90% of preterm neonates receiving PRBCT in the first week of life,[1,2] many were excluded to avoid previous transfusion-related immunologic insults. Additionally, the study focused solely on stable, growing preterm neonates to minimise confounding effects from sepsis or significant patent ductus arteriosus that could have impaired haemodynamics and contributed to TANEC. Consequently, the results may not apply to unstable preterm neonates who are at greater risk for GI complications. Finally, limitations in splanchnic NIRS monitoring, such as influences from peristalsis, stool interference, sensor variability, sensor placement, weight, gestational age, and postnatal age, must be acknowledged.[19] These variables can cause fluctuations in data, complicating clinical interpretation. Thus, the authors focused on overall patterns of oxygenation indices over time rather than isolated time-point measurements, thereby providing

meaningful conclusions while minimising confounding influences associated with TANEC.

CONCLUSION

Blood transfusion increased both cerebral and splanchnic oxygenation in VLBW neonates. Enteral feeding practices during PRBCT did not significantly influence splanchnic oxygenation. However, the decline in splanchnic oxygenation observed within the first hour of transfusion among neonates who continued feeding is thought–provoking. Undoubtedly, withholding enteral feeding has consequences, such as disruption of optimal nutrition and the need for intravenous access. Therefore, large-scale, methodologically rigorous studies are warranted to further clarify the complex interplay between enteral feeding, transfusion, and tissue oxygenation.

Appendix 1: Thresholds for PRBCT in neonates and very preterm infants.

Postnatal age	Critical illness[a] haemoglobin (g/dL)	No critical illness haemoglobin (g/dL)
Postnatal 1 week	11	10
Postnatal 2 weeks	10	8.5
Postnatal ≥3 weeks	8.5 (9)**	7

Neonates were transfused at a dose of 15-20 ml/kg for four hours to correct anaemia of prematurity if the haemoglobin levels met the following transfusion thresholds based on postnatal weeks and having a critical illness. Chart adapted from transfusion guidelines for neonates by Gilmore et al.[2] and for very preterm neonates by Deschmann et al.[11]

***Haemoglobin (Hb) level in parentheses represents the threshold level of haemoglobin for very preterm neonates born <30 gestational weeks.[a]Critical illness in a neonate refers to the need for respiratory support of high flow nasal cannula (HFNC) ≥4 L and/or FiO_2 ≥30%, and/or haemodynamic instability.[16] The definition of respiratory support in a preterm infant born <30 gestational weeks refers to the need for invasive mechanical ventilation,* continuous positive airway pressure (*CPAP) and/or non-invasive positive pressure ventilation (NIPPV), or HFNC ≥1 L/minute.[17]*

ETHICAL APPROVAL:

The study protocol was approved by Akdeniz University's Ethical Committee for Clinical Studies (Approval No. KAEK-737; Dated: 23.09.2020) and registered on ClinicalTrials.gov (Identification No. NCT06632314). The study adhered to the Declaration of Helsinki and followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

PATIENTS' CONSENT:

Written informed consent was obtained from the legal guardians of all infants.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

HO, IK, ZK, KC: Acquisition of data.
HO, KC, SA: Conception and design of the study.
HO, SA, KC: Drafting of the manuscript.
HO, IK, ZK, KC, SA: Analysis or interpretation of the data and critical revision of the manuscript for important intellectual content.
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