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Original Article

Perioperative nutrition in extremely preterm infants undergoing surgery for patent ductus arteriosus

Vera Westin [a, b, *], Mireille Vanpée [c, d], Mikael Norman [a], Elisabeth Stoltz Sjöström [e]

[a] Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden
[b] Department of Clinical Nutrition, Karolinska University Hospital, Stockholm, Sweden
[c] Department of Women and Child Health, Karolinska Institutet, Stockholm, Sweden
[d] Department of Neonatology and Department of Hospital Managed Advanced Home Care, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden
[e] Department of Food, Nutrition and Culinary Science, Umeå University, Umeå, Sweden

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S U M M A R Y

Background and aims: Patent ductus arteriosus is a common neonatal morbidity affecting more than half of infants born extremely preterm. Suboptimal nutrition in extremely preterm infants in general has been demonstrated in recent studies. The aim of this study was to describe perioperative nutritional practices in Swedish neonatal intensive care units caring for extremely preterm infants undergoing surgery for patent ductus arteriosus.
Methods: Daily enteral and parenteral nutritional intakes during the perioperative week starting three days prior and ending three days after surgery were retrospectively evaluated in five University hospitals caring for infants born <27 weeks of gestation, between 2004 and 2007.
Results: In total, 132 infants and data from 912 perioperative days were included. Mean daily energy intakes during the perioperative week (range 78–105 kcal/kg/day) varied significantly between hospitals, with the lowest intakes on the day of surgery (range 54–87 kcal/kg/day). Mean daily protein intakes during the perioperative week did not vary (range 2.3–2.6 g/kg/day) but did differ on the day of surgery (range 1.5–2.4 g/kg/day). Median parenteral (range 33–99 mL/kg/day) and enteral (range 34–123 mL/kg/day)

Abbreviations: EPT, extremely preterm infants; EXPRESS, extremely preterm infants in Sweden study; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus.

* Corresponding author. Department of Clinical Science, Intervention and Technology, Karolinska Institutet, SE-141 86, Stockholm, Sweden.
E-mail address: dievere.westin@ki.se (V. Westin).

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fluid intakes during the perioperative week, as well as median parenteral contents of energy and protein, varied significantly between hospitals.

Conclusions: Current recommended nutritional goals for extremely preterm infants were not met in the studied neonatal intensive care units. Suboptimal nutrition may have implications for short and long-term outcomes. Improved adherence to nutritional guidelines is warranted for these patients.

1. Introduction

Patent ductus arteriosus (PDA) is a common neonatal morbidity affecting approximately 60% of extremely preterm (EPT) infants [1]. Delayed closure of the ductus arteriosus has been associated with increased risk of necrotising enterocolitis, neonatal brain injury and bronchopulmonary dysplasia [2,3]. Therefore, infants with a haemodynamically significant PDA often undergo pharmacological treatment and/or surgery [1]. Although PDA-surgery effectively closes the open duct, it has not been associated with improved outcomes such as reduced incidence of bronchopulmonary dysplasia and necrotizing enterocolitis [4].

There are many reasons why obtaining nutritional goals in EPT infants is difficult and the existence of a hemodynamically significant PDA represents one of them. Nutritional intakes during the early neonatal period (days 0–6) consist mainly of parenteral nutrition and often have lower nutritional contents compared to nutritional intakes during later- (days 7–27) and postneonatal (≥28 days) periods [5,6]. International and national nutritional guidelines [5,7,8] do not provide transition strategies concerning parenteral nutrition and enteral nutrition nor do the guidelines provide information regarding nutritional management for EPT infants undergoing PDA-surgery [9].

Higher fluid intakes during the first week of life increase the risk for PDA [10], which might interfere with the possibility to reach nutritional goals. A large PDA can decrease postprandial perfusion of the superior mesenteric artery and aggravate feeding intolerance [11] delaying time to full enteral feeds [12]. Withholding enteral feeds is a common clinical practice in many neonatal intensive care units (NICUs) due to gastrointestinal side effects caused by pharmacological treatment of PDA [13]. However, minimal enteral feeds during pharmacological treatment of PDA is reported to shorten the time to full enteral feeds [14]. Furthermore, to reach physiological preoperative stabilization, withholding enteral feeds during at least 6 h prior to PDA-surgery is recommended [15].

Infants' postnatal age and nutritional intakes when undergoing PDA-surgery vary, since its hemodynamic significance varies over time and because optimal postnatal age and indications for PDA-surgery are still debated [16]. Recent studies have demonstrated the existence of suboptimal nutrition in EPT infants in general but also during the perioperative week surrounding PDA-surgery [6,17]. Still, research in these areas is very sparse.

We hypothesized that perioperative nutrition, including intakes of energy, macronutrients and fluids during the week surrounding PDA-surgery may differ between NICUs. The aim of the present study was to describe nutritional practices in Swedish NICUs and to compare the nutritional management of each unit with international standards for minimal estimated nutritional needs in EPT infants.

2. Study population and methods

The Extremely Preterm Infants in Sweden Study (EXPRESS) cohort includes infants born before 27 completed gestational weeks during 2004 and 2007 [18]. All infants who survived >24 h after birth and were affected with a hemodynamically significant PDA leading to surgery, were included in the current study (n = 141). Nutritional data for 12 days (1.2%) regarding five included infants was missing due to death (n = 1, 2 days), incomplete nutritional data (n = 3, 9 days) and transfer to county hospital (n = 1, 1 day). One infant was excluded due to unobtainable nutritional data. Infants (n = 8) who underwent PDA-surgery during early neonatal period (days 0–6) were excluded, due to expected lower nutritional intakes during this period compared to later periods [5,6]. The final study population consisted of 132 infants.

In Sweden, there are seven University hospitals with high-qualified perinatal care, to which care of EPT infants is centralized. PDA-surgery was performed in five of these seven NICUs during the years 2004–2007. We blinded the names of the NICUs and identified them with alphabetic characters (A, B, C, D and E). Three infants treated at hospitals without surgical practice were transferred to NICU A (n = 1) and NICU C (n = 2) for surgery. Due to the low number of infants at NICU D (n = 9) and the large similarity of nutritional regimens and infant characteristics with NICU E (n = 29), we decided to couple these NICUs into one unit including 38 infants, henceforth called NICU D, Table 1. Median postnatal age at PDA-surgery was 21 days (range 7–93 days).

3. Data collection

Perinatal and morbidity data within the EXPRESS cohort were prospectively registered in the Swedish neonatal quality register by physicians and nurses and has previously been published [1,18],

Table 1

Characteristics of extremely preterm infants in Sweden who underwent surgery for patent ductus arteriosus in 2004–2007, stratified by neonatal intensive care unit. Values are presented as numbers, mean ± standard deviation or median [25th;75th] percentiles.

	NICU A n = 39	NICU B n = 35	NICU C n = 20	NICU D n = 38	Total n = 132	p-value
Infant data						
22–23 weeks, n	9	6	3	10	28	0.69
24 weeks, n	9	17	6	13	45	0.14
25 weeks, n	11	9	8	11	39	0.73
26 weeks, n	12	4	4	4	24	0.08
Gestational age	24.9 ± 1.3	24.7 ± 0.8	25.0 ± 0.9	24.7 ± 09	24.8 ± 1.0	0.55
Male sex, n	25	16	14	24	79	0.24
Birth weight, g	716 ± 180	739 ± 142	750 ± 140	691 ± 161	720 ± 159	0.48
Birth weight, SDS	−0.87 ± 1.28	−0.28 ± 0.69	−0.56 ± 0.69	−0.84 ± 1.59	−0.66 ± 1.20	0.13
SGA at birth, n	6	0	1	7	14	0.04
PDA treatment						
Pharmacological treatment before surgery, n	12[a]	30	16	30	88	<0.001
Postnatal age at PDA-surgery						
7–27 days, n	22	25	16	34	97	0.01
≥28 days, n	17[b]	10	4	4[b]	35	0.01
Postnatal day of surgical treatment	23 [17; 41]	23 [15; 29]	17 [11; 25]	20 [12; 24]	21 [14; 29]	0.02
Mortality and Morbidity, days 0–70						
Death, n	0	2	0	2	4	0.35
BPD severe, n	17	11	6	15	49	0.59
IVH grade 3–4, n	5	5	2	5	17	0.98
ROP stage 3–5, n	16[b]	24[b]	12	16	68	<0.001
NEC-surgery, n	1	2	2	0	5	0.25
Any sepsis, n	13[b,c]	30[c]	10[c]	28[b]	81	<0.001

NICU, neonatal intensive care unit; SDS, standard deviation score; SGA, small for gestational age; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia (severe: oxygen >30% at 36 weeks); IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis. Significant p-values (<0.05) indicate differences between NICUs (ANOVA and Kruskal–Wallis, respectively).

[a] Significantly different from all other NICUs.

[b] Significantly different between two NICUs.

[c] Significantly different from NICU B.

nutritional intakes regarding infants who underwent PDA-surgery has also been published [17]. Briefly, detailed nutritional intakes were retrospectively obtained from hospital records for the perioperative week from three days pre-surgery (- 3 days), day of surgery (day 0) to three days post-surgery (+3 days). Nutritional data was registered and stored in a nutrition calculating software program (www.nutrium.se, Nutrium AB, Umeå, Sweden) by dieticians [6,19,20]. Nutritional data included all enteral nutrition (mothers' own milk, donor human milk, human milk fortifiers, oral supplements of micronutrients) and parenteral nutrition, glucose infusions and added electrolytes. Blood products, such as erythrocytes and plasma were not included in the analyses.

Energy and macronutrient intakes from enteral nutrition and parenteral nutrition were calculated using information from the manufacturers and breast milk analyses [6]. Nutritional intakes of energy, macronutrients and fluids were assessed in kcal/kg/day, grams/kg/day and mL/kg/day, respectively [6,17]. Nutritional intakes during the perioperative week were compared between NICUs and to minimal estimated nutritional needs of 110 kcal/kg/day, 4 g protein/kg/day, 4.8 g fat/kg/day, and 12 g carbohydrates/100 kcal [17], based on international nutritional guidelines [7,21]. Since energy and two of three macronutrients were expressed in kg/day, minimal estimated nutritional needs of carbohydrates were changed from 12 g/100 kcal [17] to 13.2 g/kg/day based on minimal estimated energy needs of 110 kcal/kg/day. To facilitate evaluation of fluid intakes, this was compared to estimated needs of fluid of 160 mL/kg/d [10]. Concentration of energy (kcal/100 mL) and protein (grams/100 mL) regarding enteral nutrition and parenteral nutrition were calculated and compared to contents of premature formula (80 kcal/100 mL, 2.9 g protein/100 mL) [22] and "all-in-one-bag" parenteral solution (91 kcal/100 mL, 3.1 g protein/100 mL) [23], respectively.

Questionnaires were sent to NICUs to obtain information about nutritional management and if each NICU had specific guidelines regarding the week surrounding PDA-surgery.

4. Statistical analyses

Normally distributed variables were reported as means and standard deviation (SD) and non-parametric continuous variables were reported as median and interquartile ranges (IQRs). Categorical measures were summarized as dichotomous variables. All analyses were performed using Stata/IC 14.2 software (StataCorp LP, College Station, Texas, USA). We used one-way ANOVA between groups with post-hoc tests for parametric data, when comparing the four Swedish NICUs (NICU A, B, C, D). For non-parametric data such as enteral nutrition and parenteral nutrition intakes Kruskal–Wallis test was used. Paired sampled t-test and Wilcoxon signed-rank test were performed to compare third day prior (day −3) and post (day +3) PDA-surgery regarding parametric- and non-parametric data, respectively. Multiple linear regression was used to disentangle the role of NICU-specific management from other factors that could affect perioperative nutritional intakes such as gestational age, small for gestational age at birth, pharmacological treatment before surgery, any sepsis and neonatal week of PDA-surgery. Since the number of infants was highest at NICU A, this NICU was chosen as reference in the regression analyses when comparing energy and protein intakes to other NICUs. P-value <0.05 was considered as statistically significant.

5. Ethical approval

This study was approved by the regional ethical vetting board at Lund University, Sweden (Dnr 42/2004 and 138/2008).

6. Results

Table 1 illustrates the cohort's characteristics stratified by NICU. There were significant differences between NICUs regarding the proportions of infants that were small for gestational age at birth and that were pharmacologically treated before surgery. The postnatal age at PDA-surgery and incidence of sepsis varied between NICUs.

7. Nutritional intakes

7.1. Energy

Total mean daily energy intake calculated for the whole perioperative week in comparison with minimal estimated nutritional needs provided by international guidelines (110 kcal/kg/day), was 95%, 71%, 84% and 90%, at NICUs A, B, C and D, respectively, Table 2. The number of infants meeting the minimal estimated nutritional needs of 110 kcal/kg/day was 9 (24%), 1 (3%), 1 (6%) and 10 (26%) infants at NICUs A, B, C and D, respectively. During the day of surgery (day 0), the energy deficit was pronounced in all hospitals and ranged from 23 to 56 kcal/kg/day below minimal requirements, Fig. 1A. Energy intakes postsurgical (+3 days) compared to pre-surgical (- 3 days) were significantly decreased at NICUs B and C, by 16 kcal/kg/day (95% CI: 5–28; $p = 0.003$) and by 12 kcal/kg/day (95% CI: 1–22; $p = 0.01$), respectively, Fig. 1A.

7.2. Protein

Total mean daily protein intake calculated for the whole perioperative week in comparison with minimal estimated nutritional needs provided by international guidelines (4 g/kg/day), was 65% at NICUs A, C and D, and 58% at NICU B, Table 2. None of the infants met the minimal estimated nutritional needs of 4 g/kg/day. During the day of surgery (day 0), the protein deficit was pronounced in all hospitals and ranged from 1.6 to 2.5 g/kg/day below minimal requirements, Fig. 1B. Protein intakes postsurgical (+3 days) compared to pre-surgical (- 3 days) were significantly decreased at NICU B, by 0.4 g/kg/day (95% CI: 0.1–0.8; $p = 0.009$), Fig. 1B.

Table 2
Perioperative (day of surgery ± 3 days) energy, macronutrient and fluid intakes in extremely preterm infants who underwent surgery for patent ductus arteriosus, stratified by neonatal intensive care unit and for total, enteral and parenteral intakes. Values are presented as mean ± standard deviations and regarding enteral and parenteral nutrition as median [25th;75th] percentiles.

	NICU A N = 38	NICU B N = 34	NICU C N = 17	NICU D N = 38	P-value	Min-needs[a]
Macronutrient intake						
Energy						
Total, kcal/kg/day	105 ± 13	78 ± 13	92 ± 10	99 ± 18	<0.001	110
Enteral, kcal/kg/day	95 [82; 103]	18 [5; 47]	48 [41; 63]	64 [35; 84]	<0.001	
Parenteral, kcal/kg/day	10 [7; 15]	53 [35; 66]	39 [31; 50]	36 [23; 52]	<0.001	
Protein						
Total, grams/kg/day	2.6 ± 0.5	2.3 ± 0.5	2.6 ± 0.4	2.6 ± 0.4		4
Enteral, grams/kg/day	2.3 [1.8; 2.6]	0.5 [0.1; 1.1]	1.3 [1.0; 1.8]	1.6 [0.9; 2.1]	<0.001	
Parenteral, grams/kg/day	0.2 [0.1; 0.4]	1.9 [1.0; 2.1]	1.2 [1.0; 1.5]	1.0 [0.5; 1.6]	<0.001	
Fat						
Total, grams/kg/day	5.4 ± 0.9	3.5 ± 1.3	3.8 ± 0.9	4.0 ± 1.9	<0.001	4.8
Enteral, grams/kg/day	5.0 [4.5; 5.7]	1.0 [0.2; 2.5]	2.8 [2.2; 3.3]	3.3 [1.7; 4.6]	<0.001	
Parenteral, grams/kg/day	0.2 [0.1; 0.3]	1.9 [1.3; 2.9]	0.9 [0.6; 1.3]	0.5 [0; 1.0]	<0.001	
Carbohydrates						
Total, grams/kg/day	11.1 ± 0.9	9.2 ± 1.6	11.0 ± 1.2	12.7 ± 1.5	<0.001	13.2
Enteral, grams/kg/day	8.9 [7.5; 9.9]	1.7 [0.5; 3.9]	4.5 [3.7; 6.3]	5.9 [3.5; 7.8]	<0.001	
Parenteral, grams/kg/day	2.0 [1.3; 2.9]	6.6 [4.5; 8.7]	5.8 [5.3; 7.3]	6.7 [4.5; 9.1]	<0.001	
Fluids						
Total, mL/kg/day	158 ± 13	122 ± 11	158 ± 10	185 ± 21	<0.001	160
Enteral, mL/kg/day	130 [106; 142]	26 [7; 60]	64 [54; 89]	92 [55; 120]	<0.001	
Parenteral, mL/kg/day	26 [18; 43]	93 [62; 109]	87 [76; 107]	93 [72; 120]	<0.001	

NICU, neonatal intensive care unit. P-values indicate differences between NICUs (ANOVA and Kruskal–Wallis regarding total energy- and macronutrients intake and enteral/parenteral energy- and macronutrients intake, respectively).
[a] Min-needs = Minimal estimated nutritional needs for enteral and parenteral nutrition [14,19].

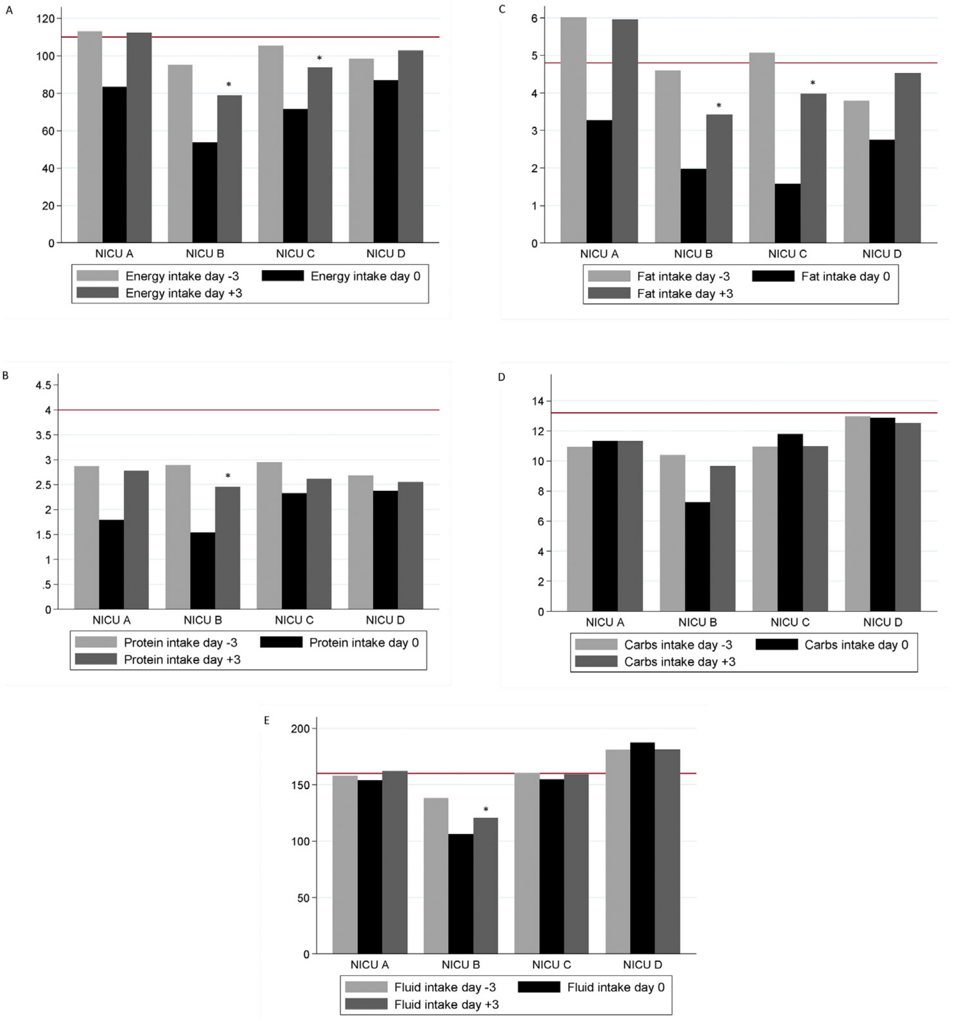

Fig. 1. Mean values for A) energy-, B) protein-, C) fat-, D) carbohydrates-, and E) fluid intakes pre-surgical (day −3), on the day of surgery (day 0) and postsurgical (day +3) ligation for patent ductus arteriosus in extremely preterm infants, stratified by neonatal intensive care unit. Red lines denote the reference value for minimal estimated nutritional needs of 110 kcal/kg/d, 4.0 g protein/kg/d, 4.8 g fat/kg/d, 13.2 g carbohydrates/kg/d and 160 mL fluid/kg/d [7,19]. *Statistically significant difference between pre-surgical (day −3) and postsurgical (day +3) days.

7.3. Fat

Total mean daily fat intake calculated for the whole perioperative week in comparison with minimal estimated nutritional needs provided by international guidelines (4.8 g/kg/day) was 112%, 73%, 80% and 84%, at NICUs A, B, C and D, respectively, Table 2. The number of infants meeting the minimal estimated nutritional needs of 4.8 g/kg/day was 28 (74%), 4 (12%), 1 (6%) and 13 (34%) infants at NICUs A, B, C and D, respectively. During the day of surgery (day 0), the fat deficit was pronounced in all hospitals and ranged from 1.5 to 3.2 g/kg/day below minimal requirements, Fig. 1C. Fat intakes postsurgical (+3 days) compared to pre-surgical (- 3 days) were significantly decreased at NICUs B and C, by 1.2 g/kg/day (95% CI: 0.2–2.1; $p = 0.007$) and by 1.1 g/kg/day (95% CI: 0.1–2.1; $p = 0.01$), respectively, Fig. 1C.

7.4. Carbohydrates

Total mean daily carbohydrate intake calculated for the whole perioperative week in comparison with minimal estimated nutritional needs provided by international guidelines (13.2 g/kg/day), was 84%, 70%, 83% and 96%, at NICUs A, B, C and D, respectively, Table 2. The number of infants meeting the minimal estimated nutritional needs of 13.2 g/kg/day was 0, 0, 1 (6%) and 12 (32%) infants at NICUs A, B, C and D, respectively. During the day of surgery (day 0), the carbohydrate deficit was pronounced in all hospitals and ranged from 0.3 to 6.0 g/kg/day below minimal requirements, Fig. 1D. At all NICUs, no differences were seen between carbohydrate intakes postsurgical (+3 days) compared to pre-surgical (- 3 days), Fig. 1D.

7.5. Fluids

Total mean daily fluid intake calculated for the whole perioperative week was in comparison with minimal estimated nutritional needs provided by international guidelines (160 mL/kg/day), 99% at NICUs A and C, and 76% and 116% at NICUs B and D, respectively, Table 2. During the day of surgery (day 0), the total fluid ranged from 54 below to 27 mL/kg/day above minimal requirements, Fig. 1E. Differences between NICUs regarding total fluid intakes postsurgical (+3 days) compared to pre-surgical (- 3 days) were small except for NICU B at which total fluid intake + 3 days compared to - 3 days was significantly decreased by 18 mL/kg/day (95% CI: 7–28; $p = 0.001$), Fig. 1E.

7.6. Enteral fluid

Median enteral fluid intake during perioperative week in comparison to NICU A was 20%, 49% and 71%, at NICUs B, C and D, respectively, Table 2. At NICUs A, B, C and D, the proportions of enteral fluids of the total fluid intake during perioperative week were 82%, 21%, 41% and 49%, respectively, Table 2. Median enteral fluid intake during the day of surgery (day 0) was 73 mL/kg/day (IQR: 39–98 mL/kg/day), 0 mL/kg/day (IQR: 0–2 mL/kg/day), 19 mL/kg/day (IQR: 0–35 mL/kg/day) and 53 mL/kg/day (IQR: 31–76 mL/kg/day) at NICUs A, B, C and D, respectively, Fig. 2. Intake of enteral fluid on postsurgical (+3 days) compared to pre-surgical (- 3 days) was significantly decreased by 27 mL/kg/day ($p < 0.001$) and by 24 mL/kg/day ($p = 0.04$) at NICUs B and C, respectively. In contrast, intake of enteral fluid on

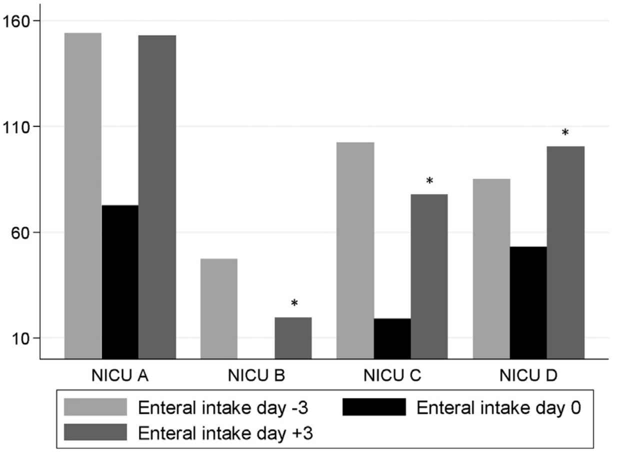

Fig. 2. Median values for enteral fluid intakes pre-surgical (day −3), on the day of surgery (day 0) and postsurgical (day +3) ligation for patent ductus arteriosus in extremely preterm infants, stratified by neonatal intensive care unit. *Statistically significant difference between pre-surgical (day −3) and postsurgical (day +3) days.

postsurgical (+3 days) compared to pre-surgical (- 3 days) was significantly increased at NICU D by 16 mL/kg/day ($p = 0.05$), Fig. 2.

7.7. Energy and protein concentrations in enteral feedings and parenteral fluids

Differences between the NICUs during the perioperative week for median enteral energy- and protein concentrations were small, Table 3. The highest values were still below the guidelines for enteral energy and protein concentrations, by 7% and by 38%, respectively. In contrast, median parenteral energy- and protein concentrations during perioperative week differed significantly between NICUs and the highest values were still below the guidelines for parenteral energy and protein concentrations, by 36% and by 39%, respectively.

7.8. Multiple linear regression regarding energy and protein intakes

The difference in mean energy and protein intakes during perioperative week between hospitals remained after adjusting for gestational age, small for gestational age, pharmacological treatment before PDA-surgery, any sepsis and postnatal week of PDA-surgery, Table 4.

Table 3
Perioperative (day of surgery ± 3 days) median energy- and protein concentrations in enteral feeds and parenteral fluids in Swedish extremely preterm infants who underwent surgery for patent ductus arteriosus, stratified by neonatal intensive care unit. Values are presented as median [25th;75th] percentiles.

	NICU A N = 38	NICU B N = 34	NICU C N = 17	NICU D N = 38	P-value	Ref[a]
Concentrations						
Enteral feedings						
Energy, kcal/100 mL	72 [71; 76]	73 [68; 76]	74 [72; 80]	68 [64; 73]	<0.001	80
Protein, grams/100 mL	1.8 [1.5; 1.9]	1.8 [1.7; 1.8]	1.8 [1.7; 2.0]	1.7 [1.6; 1.8]	0.505	2.9
Parenteral fluids						
Energy, kcal/100 mL	42 [35; 44]	58 [51; 63]	45 [42; 46]	37 [30; 44]	<0.001	91
Protein, grams/100 mL	1.0 [0.7; 1.3]	1.9 [1,5; 2.2]	1.5 [1.2; 1.8]	1.1 [0.7; 1.2]	<0.001	3.1

NICU, neonatal intensive care unit.
[a] Ref, reference regarding recommended concentrations for energy and protein in enteral feedings and parenteral fluids [22,23].

Table 4
Energy- and protein intakes during perioperative week of surgery for patent ductus arteriosus in extremely preterm infants. Comparisons between neonatal intensive care units (A reference), gestational age, small for gestational age at birth, pharmacological treatment before surgery, any sepsis and postnatal week of surgery for patent ductus arteriosus.

	Energy (kcal)			Protein (grams)		
Variable	Regression coefficient	95% CI	p-value	Regression coefficient	95% CI	p-value
NICU A	(Reference)			(Reference)		
NICU B	−23.98	−32.05, −15.92	<0.001	−0.42	−0.68, −0.16	0.002
NICU C	−8.17	−17.08, 0.73	0.072	−0.02	−0.31, 0.27	0.884
NICU D	−1.97	−9.49, 5.56	0.605	−0.14	−0.39, 0.11	0.266
Gestational age	−2.78	−5.23, −0.33	0.027	−0.06	−0.15, 0.02	0.113
SGA at birth (weeks and days)	−2.98	−11.51, 5.55	0.490	−0.02	−0.30, 0.26	0.874
Pharmacological treatment before PDA surgery	−2.21	−8.23, 3.80	0.468	0.15	−0.05, 0.34	0.145
Any sepsis	−1.23	−6.89, 4.42	0.667	0.16	−0.03, 0.34	0.092
Postnatal week of PDA surgery	1.91	0.79, 3.02	0.001	0.01	−0.03, 0.05	0.629

CI, confidence interval; NICU, neonatal intensive care unit; SGA, small for gestational age, PDA, patent ductus arteriosus.

7.9. Questionnaire

NICU A did not return the questionnaire regarding perioperative nutritional management. According to the received replies, neither national- nor local guidelines on perioperative nutrition were available in Sweden during the investigated time period. Withholding enteral feeds for approximately 4 h before surgery was performed at NICUs B and D.

8. Discussion

Our findings demonstrate that energy- and macronutrient intakes as well as fluid intakes were below estimated nutritional needs in all NICUs in Sweden who performed PDA-surgery. In addition, the distribution between enteral- and parenteral fluid highly differed between NICUs. Energy- and protein concentrations in parenteral fluids also varied between the NICUs and the energy- and protein concentrations for both parenteral and enteral fluids were suboptimal compared to recommended concentrations [22,23].

Minimal estimated nutritional needs according to the Swedish guidelines [5], regarding the fourth postnatal day, including 50% enteral nutrition might be a better reference for infants included in our study, compared to the international references we used [7,21], since all NICUs used both enteral nutrition and parenteral nutrition during the perioperative week. Two NICUs (A, D) met minimal estimated energy needs of 100 kcal/kg/d according to the Swedish guidelines [5] during the perioperative week. Furthermore, despite parenteral nutrition, infants at all NICUs showed suboptimal protein intakes during the perioperative week by not reaching the lower boundary of 3.5 g protein/kg/day, according to these guidelines. Adequate energy intake is crucial to protein utilization and given the observed energy and protein deficit in all NICUs, protein metabolism and lean mass accretion could be negatively affected [24].

Recently Joosten et al. presented guidelines on pediatric parenteral nutrition regarding needs for energy intake [25]. According to these guidelines, withholding parenteral nutrition during one week could be considered for critically ill children, including children treated surgically in pediatric intensive care units. According to Fivez et al. withholding parenteral nutrition significantly reduced the length of the stay in the pediatric intensive care unit because of fewer infections, less days with mechanical ventilation and reduced occurrence of kidney failure [26]. However, these pediatric parenteral nutrition guidelines did not propose omission of parenteral nutrition for critically ill EPT infants. Omission of parenteral nutrition in EPT infants up to one week could be devastating. The study by Joosten et al. proposed lower parenteral energy intakes during the acute phase (45–55 kcal/kg/day) and the recovery phase (90–120 kcal/kg/day) [25], compared to previous guidelines [7,21]. In our cohort, despite partial enteral fluid intake, NICU B did not reach the lower boundary of 90 kcal/kg/day and the other NICUs never reached the upper limit of 120 kcal/kg/day. Today, the minimal estimated nutritional needs for the youngest and in particular the critically ill EPT infants are yet not known and the parenteral energy intakes proposed during the acute phase might fit this special group of infants.

Fluid intakes of 122–150 mL/kg/day during late (7–27 days) neonatal period, were considered as restricted, while fluid intakes 169–200 mL/kg/day during late neonatal period were considered as liberal, according to a Cochrane review [10]. Careful restriction of fluid, while avoiding dehydration could be expected to decrease the risk for both PDA and necrotizing enterocolitis. According to these Cochrane definitions, mean total fluid intake during the perioperative week in late neonatal period (7–27 days) was restricted at NICU B (123 mL/kg/day) and liberal at NICU D (185 mL/kg/day).

An extended transition from parenteral nutrition to enteral nutrition due to ward staff's concern to introduce and advance enteral feeds, including to start with fortifications of human milk, is a frequent cause of suboptimal nutrition in preterm infants [9,27]. Accordingly, every new period of parenteral nutrition constitutes a risk for suboptimal nutritional intakes since time to full enteral nutrition could extend to several weeks [19,27]. To assist practitioners to overcome this concern, more specific, tailored guidelines based on data-driven nutrition strategies may help. Daily feedback of a team consisted of neonatologists, nurses and dieticians is crucial in this context.

In our study, all NICUs but one (A) had a high proportion of parenteral nutrition with more than 50% parenteral nutrition during the perioperative week and even on the third day postsurgical. Of interest, at NICU A, most infants underwent surgery at a later postnatal age (≥28 days) and significantly fewer infants were affected by retinopathy of prematurity and any sepsis, compared to all other NICUs. A previous publication showed that low energy intake during the first four weeks of life was an independent risk factor for severe retinopathy of prematurity in EPT infants [28]. Early provision of energy and protein is an important priority in the clinical care of EPT infants and may reduce risk of morbidity in these infants [29]. This supports the speculation that enhanced nutrition could improve outcome and perhaps PDA-surgery at a later postnatal age could be beneficial for EPT infants. However, infants born at lower gestational age are at high risk of morbidity and it is difficult to disentangle healthy infants in a group of EPT infants born before 27 completed gestational weeks. In this group of vulnerably infants the reasons to malnutrition are difficult to establish because of many confounding factors such as low birth weight and requirement of mechanical ventilation [30]. In the EXPRESS cohort, 55% of the 1-year survivors had major neonatal morbidity [18]. Infant's health status is therefore an important factor why adequate nutritional intakes are difficult to achieve regardless of nutritional guidelines. Nevertheless, it has been shown that intakes of energy and protein are independent predictors of postnatal growth in EPT infants even after adjusting for severity of illness [6].

In our study, enteral concentrations were suboptimal in all NICUs, particularly regarding protein content. Protein concentration of human milk decreases over time and human milk expressed during the first four postnatal weeks often has higher protein concentration compared to human milk expressed after 28 days [20]. Human milk to infants undergoing PDA-surgery during post-neonatal period may need increased supplementation of human milk fortifier, particularly when fluid restriction is prescribed.

Withholding enteral nutrition preventing gastrointestinal symptoms during pharmacological treatment for PDA was clinical practice at many NICUs [13]. Consequently, EPT infants who underwent PDA-surgery were at risk for suboptimal nutrition already before surgery. According to the questionnaire that were sent out to all NICUs in this study, withholding enteral feeds before surgery during approximately 4 h was performed at NICUs B and D. When withholding enteral nutrition in connection with pharmacological treatment or surgery, it is crucial to provide adequate parenteral nutrition. NICU B had suboptimal nutrition despite the unit's highest parenteral concentrations compared to all other NICUs. The restricted total volume intake might have contributed to this as well as the parenteral energy and protein concentrations lower than the recommended content of “all-in-one-bag” parenteral nutrition [23]. In a recently published study of Hansson et al., volume restrictions with hemodynamically significant PDA were the main cause to diminished intakes of energy and protein [31]. It has been shown that a concentrated parenteral nutrition solution is an efficient way of providing early nutrition in very low birth weight infants without being associated with enhanced fluid intakes or increased infant morbidity [32]. Concentrated parenteral solutions is therefore an important nutritional strategy to prevent underfeeding during volume restriction.

In a prospective cohort study, Ng et al. proposed “nutritional bundles” including guidelines regarding feeding strategies through illness [33]. Despite high rates of morbidity among EPT infants, these “nutritional bundles” may facilitate meeting estimated nutritional needs. Other studies proposed implementation of multiple strategies to improve nutrition [34] and reduce growth restriction among very low birth weight infants. Furthermore, even for term born infants with congenital heart disease, optimal perioperative feeding strategies are unknown, which may cause large variations in perioperative feeding practice between different hospitals [35].

In our study, there were no written feeding protocols regarding perioperative nutrition available at the included Swedish NICUs, possibly illustrating the gap of knowledge and resulting in variations in nutritional intake during the perioperative week between NICUs.

Strengths of this study are the population-based cohort of EPT infants and the detailed information regarding infants' nutritional intakes. The study highlights the lack of clear guidelines and the range of clinical differences in the nutritional and fluid strategies used in Sweden. Limitations are the retrospective study design and potential inaccuracies regarding calculation of nutrient intakes due to incomplete weight data during the perioperative week. The possible associations on mortality and morbidity for the nutritional and fluid differences described have not been analyzed.

In conclusion, nutritional guidelines regarding the perioperative week surrounding PDA-surgery are warranted. The adherent application to the guidelines would improve the nutritional management and accordingly the nutritional status of EPT infants undergoing PDA-surgery.

Statement of authorship

VW had primary responsibility for protocol development, outcome assessment, preliminary data analysis and writing the manuscript. MV and MN participated in the development of the protocol and the analytical framework for the study and contributed to the writing of the manuscript. ESS supervised the design and execution of the study and contributed to the writing of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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