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Implementation of nutritional care bundle is associated with improved growth in preterm infants born before 32 gestational weeks

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ABSTRACT

Objective: To evaluate whether implementing a nutritional care bundle is associated with growth and morbidity in very preterm (VPT) infants.
Study design: This study compared 87 VPT infants (<32 gestational weeks) born 2018 (Before group) with 75 infants born 2020 (After group), treated at a single center in the Czech Republic. A nutritional care bundle was implemented during 2019.
Results: Median gestational age (weeks) was 30.0 [IQR 27.6–31.1] for the Before group and 29.9 [IQR 27.9–30.6] for the After group. During postnatal days 1–14, parenteral fluid intake was significantly lower in the After group compared to the Before group and conversely for enteral fluid intake. Infants in the After group achieved full enteral feeds by postnatal day 14 (72.9 % vs. Before group 51.9 %). Weight z-scores decreased significantly less from birth to 36 weeks postmenstrual age in the After group (−0.8 [IQR −1.3 to −0.5]) compared to the Before group (−1.5 [IQR −2.0 to −1.2]). Head circumference z-scores decreased significantly less in the After group (−0.8±0.9) than the Before group (−1.6±1.1). Decreased rate of patent ductus arteriosus (PDA) requiring treatment was observed in the After group ($P < 0.001$).
Conclusions: Implementation of a nutritional care bundle in VPT infants was associated with improved postnatal growth and may reduce treatment-requiring PDA.

1. Introduction

Preterm infants born before 32 completed weeks of gestation (very preterm; VPT) are at risk for malnutrition, growth failure, and neonatal morbidity, especially those infants born extremely preterm (<28 weeks of gestation) [1–3]. Nutritional optimization may significantly influence morbidity and growth outcomes in preterm infants [4–6]. However, adequate nutrition is challenging due to the limited nutrient stores and high nutrient requirements in this patient population [7,8]. Mother's own breast milk is the preferred choice for enteral feeding in preterm infants, and donor breast milk is the second choice [9]. To meet the high nutritional requirements of preterm infants, an individualized approach to human milk fortifiers has been proposed [10–12]. Due to intestinal immaturity, premature infants weighing <1500 g (very low birth weight) often receive parenteral nutrition until full enteral nutrition can be achieved [9,13]. Adequate protein and energy intake through parenteral nutrition can significantly improve postnatal growth in VPT infants [6,14]. Neonatal intensive care units (NICUs) use a variety of methods to administer parenteral nutrition, including individualized pharmacy-prepared parenteral solutions and a commercially available triple-chamber bag [15]. A moderate early restrictive fluid management approach is recommended in VPT infants to reduce the incidence of patent ductus arteriosus (PDA), with fluid intake gradually increased [16,17], but this strategy might lead to reduced energy and nutrient intake, which can negatively affect an already faltering growth. Therefore, a software-based nutrition calculation system could be an important tool to optimize nutritional care in the NICU [18]. This calculation system allows for an individualized approach to nutrient intake in preterm infants, resulting in improved growth [19,20].

In the present study, we hypothesized that infants would have

Abbreviations and acronyms: AG, After group; BG, Before group; DOL, Day of life; IQR, Interquartile range; NICU, Neonatal intensive care unit; PDA, Patent ductus arteriosus; PMA, Postmenstrual age; VPT, Very preterm.

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smaller decreases in standard deviation scores (z-scores) for weight, length, and head circumference from birth to 36 weeks postmenstrual age (PMA) and lower rates of treatment-requiring PDA following implementation of multifaceted nutritional care bundle compared to infants born before the bundle was implemented.

2. Methods

This study was designed as a retrospective observational before-and-after study, comparing two cohorts of VPT infants born before 32 completed weeks of gestational age and treated at the tertiary NICU in České Budějovice, Czech Republic. The Before group (BG) included all infants ($n = 87$) born between January 1, 2018, and December 31, 2018. The After group (AG) included all infants ($n = 75$) born between January 1, 2020, and December 31, 2020. The study was approved by the local Ethics Committee for Clinical Trials at the Hospital in České Budějovice (no. 107/20), and legal guardians gave their written consent to participate in the study.

Infants who did not survive the first 24 h after birth and infants with major congenital malformations known to affect growth were excluded. Infants diagnosed with necrotizing enterocolitis or spontaneous intestinal perforation were excluded due to expected interference with enteral nutrition, and infants with hydrocephalus were excluded due to expected aberrant growth. A total of 79 infants in the BG and 70 infants in the AG were included in the analyses, the flowchart of the study groups is shown in Fig. 1. In each group, three infants died, and three infants were transferred to a lower-level hospital during the first 14 days after birth.

2.1. Nutritional care bundle

A change in the nutritional regimen in the NICU was implemented in the course of 2019. The following changes were made: 1) Introduction of a highly concentrated commercial parenteral nutrition [6] solution; 2) Introduction of targeted individualized fortification of breast milk with regular analysis of breast milk energy and macronutrient content 3) Daily use of a software-based nutrient calculation system [19] of individual nutrient components with comparison of variations in nutrition and anthropometric measurements according to the recommended nutrient intakes and changes in growth (z-score); 4) A weekly multidisciplinary nutrition round.

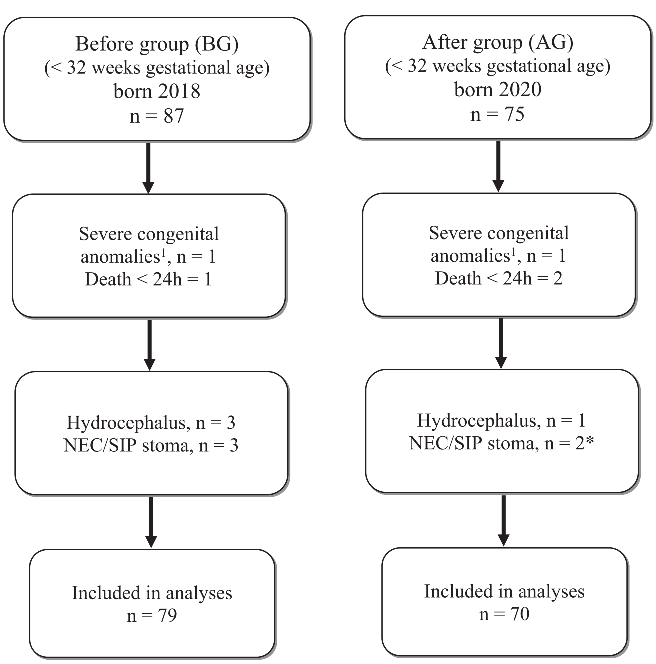

Fig. 1. Flowchart of included and excluded infants.
[1]Hydrops fetalis, heart malformation.
*One infant with two diagnoses (NEC and hydrocephalus).
NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation.

Standard practice in the NICU during both study periods was to use mother's own breast milk if available. Otherwise, donor breast milk was used, and minimal enteral feedings were initiated from the day of birth. Enteral feedings were increased by 20–30 mL/kg/d in BG and by 30 mL/kg/d in AG, according to tolerance. Mother's own breast milk was administered unpasteurized, and donor's breast milk was administered after bacteriological analysis and after being routinely heat-treated using Holder pasteurization. Breast milk analysis for energy and macronutrients was performed by using mid-infrared spectrophotometry (Miris 08–02–102-1.0). In both groups, fortification of breast milk was started after day of life (DOL) seven if 75 % of the daily fluid intake was given enterally.

In the BG, during 2018, target total fluid intake was 180 mL/kg/d. Parenteral nutrition was comprised of an individualized pharmacy-prepared all-in-one solution bag. Even though breast milk analyses were sporadically performed in this group, the results of these analyses were not incorporated in a nutritional calculation and no adjustments of fortification were made based on the results. Individualized fortification of breast milk was not practiced during 2018 in the NICU, and it was added when the enteral intake reached 100 mL/kg/d. Calculations of nutritional intake were made at the discretion of the attending physician.

In the AG, during 2020, target total fluid intake was 150 mL/kg/d. A commercially available concentrated triple-chamber parenteral nutrition solution was used (Numeta G13, Baxter Medical AB, Stockholm, Sweden). This solution has previously shown to optimize macronutrient intakes [6]. Mother's own breast milk was analyzed for energy and macronutrient content, first at DOL 15, then once weekly. Donor breast milk was always analyzed for energy and macronutrient content. If analysis of mother's own breast milk was not available during the first 14 postnatal days, the average content of breast milk samples from mothers of extremely preterm infants was used in the nutrient calculations [21]. Supplementation with human milk fortifiers (fortification) was individualized based on breast milk analysis and relevant blood and metabolic markers analyzed once a week. In practice, the specific macro-and/or micronutrient that was shown to be deficient was supplied [11], so that optimal nutritional intakes according to the latest ESPGHAN recommendations were maintained [9]. A software-based nutrition calculation system - Nutrium (Nutrium AB, Umeå, Sweden) - was used daily to calculate fluid and nutrient intakes, including breast milk analysis. The nutritional software allowed the optimization of the proportions of nutrients administered enterally and parenterally while maintaining the recommended amounts of macronutrients, micronutrients, and fluid volume. Priority was given to enteral intakes, according to the tolerance of the infant. Parenteral nutrition was subsequently supplemented until optimal nutrition recommendations were achieved [13]. A once-weekly multidisciplinary nutrition round was instated where the nutritional status of patients was presented and discussed. The goal was to support the nutritional care of the infants, providing nutrition according to the latest recommendations and optimizing growth. The rounds were attended by physicians and nurses (including breast milk bank nurses).

Study outcomes were change in z-scores for weight, length, and head circumference from birth to 36 weeks PMA and change in the occurrence of treatment-requiring PDA after the nutritional care bundle was implemented.

2.2. Data collection

For both groups, fluid intakes (mL/kg) were registered daily for DOL 1–14. Day of birth was omitted due to different lengths of day. For the BG, fluid intakes were obtained from patient records, while for the AG, fluid intakes were obtained from registrations in the software-based nutrition calculation system. The volume of administered blood products was not included in the calculations. Birth weight was used for fluid calculations until the current weight had surpassed birth weight; thereafter, current weight was used. Weight and head circumference were measured in both groups at birth, once weekly at DOL 7, 14, and 21, and at 36 weeks PMA. Length in both groups was registered at birth and at 36 weeks PMA. Fenton growth reference (22) was used to calculate z-scores for weight, head circumference and length. Anthropometric data for the BG were obtained from medical records, and z-scores for weight, head circumference and length were determined retrospectively. Anthropometric data for the AG were prospectively collected in the NICU using the software-based nutrition calculation system, which automatically calculated z-scores for weight, head circumference and length. Only infants with complete anthropometric measurements at all time points were included in the growth analyses (BG, $n = 42–43$; AG, $n = 37$).

Perinatal and morbidity data for both groups were prospectively collected in a database resembling the Swedish Neonatal Quality Register (https://www.medscinet.com/PNQ/). Data obtained included gestational age at birth, sex, antenatal corticosteroid treatment, delivery mode, multiple pregnancy, mechanical ventilation treatment, treatment of PDA, postnatal corticosteroid treatment, insulin, inotrope and surfactant treatments, hydrocephalus, congenital malformations, hydrops fetalis, spontaneous intestinal perforation, necrotizing enterocolitis, and sepsis.

2.3. Statistical analyses

Analyses were performed using IBM SPSS Statistical software (version 27.0; IBM, Armonk, New York, USA). For comparison between the BG and AG, Independent Samples *t*-test and Mann-Whitney *U* Test were used for continuous variables as appropriate, and Fischer's Exact Probability Test was used for categorical variables. Continuous variables were expressed as mean±SD or median and interquartile range (IQR, presenting 25th–75th percentiles), depending on the distribution of data. Categorical variables were expressed in numbers and percentage. $P < 0.05$ was considered significant.

3. Results

The median gestational age was 30.0 weeks in the BG and 29.9 weeks in the AG. There were no significant differences in baseline characteristics between the two groups, Table 1.

3.1. Fluid intake

Total fluid intake during the different time periods is shown in Table 2. Total fluid intake was significantly higher in the BG compared to the AG on DOL 1 through 4, 11, and 13, Fig. 2.

Total parenteral fluid intake during the different time periods is shown Table 2. Parenteral fluid intake was significantly lower in the AG on every single day during the period DOL 1 through 14, Fig. 2.

Total enteral fluid intake during the different time periods is shown in Table 2. Enteral fluid intake was significantly higher in the AG on every single day during the period DOL 1 through 14, Fig. 2. During the same period, a higher percentage of infants in the AG (72.9 %) achieved total enteral feeds compared to the BG (51.9 %; $P = 0.009$).

3.2. Growth

Compared to the BG ($n = 42$), weight z-score decreased significantly less from birth to 36 weeks PMA in the AG ($n = 37$; −1.51 (IQR −2.0 to −1.18) vs. -0.83 (IQR −1.27 to −0.5), $P < 0.001$, Mann-Whitney *U* Test). The same was observed for mean±SD change in head circumference z-score from birth to 36 weeks PMA in the BG ($n = 43$; −1.55±1.1) vs. the AG (n = 37; −0.83±0.86, $P = 0.001$, Independent Samples *t*-test). Furthermore, similar results were noted for mean±SD change in length z-score from birth to 36 weeks PMA, however without statistical significance (BG (n = 43): −1.84±1.0 vs. AG (n = 37): −1.49±0.85, $P = 0.1$, Independent Samples t-test).

Fig. 3 depicts the weight and head circumference z-scores in the two groups during the admission period. In the BG, weight and head circumference z-scores decreased throughout the admission period, while in the AG, both measurements increased from DOL 21 and

Table 1
Baseline characteristics in very preterm infants born before (Before group, born in 2018) and after (After group, born in 2020) implementation of a nutritional care bundle. Data shown in median, IQR, mean, SD or percent (%).

Characteristics	Before group, *N* = 79		After group, *N* = 70	P value	
	Median	IQR	Median	IQR	
Gestational age, weeks	30.0	27.6–31.1	29.9	27.9–30.6	0.582[a]
Birth weight, grams	1250	890–1590	1310	945–1517.5	0.974[a]
Birth weight, SDS	−0.06	−0.63 to 0.23	−0.06	−0.57 to 0.56	0.488[a]
Birth head circumference, cm	27.0	24.0–28.0	26.0	23.9–28.0	0.641[a]
	Mean	SD	Mean	SD	
Birth head circumference, SDS	−0.3	±0.87	−0.45	±0.96	0.343[b]
Birth length, cm	37.1	±4.3	36.8	±3.9	0.682[b]
Birth length, SDS	−0.2	±0.9	−0.4	±0.9	0.459[b]
	N (%)		N (%)		
Sex, male	47 (59.5)		42 (60.0)	0.542[c]	
Antenatal steroid treatment	48 (60.8)		48 (68.6)	0.206[c]	
Cesarean section	63 (79.7)		56 (80.0)	0.567[c]	
Multiple pregnancy	17 (21.5)		23 (32.9)	0.085[c]	

Excluded from analyses: infants with necrotizing enterocolitis, spontaneous intestinal perforation, hydrocephalus, congenital malformations, hydrops fetalis. IQR, interquartile range presented as 25th – 75th percentiles; SDS, standard deviation score.

[a] Mann-Whitney *U* Test.
[b] Independent Samples *t*-test.
[c] Fisher's Exact Probability Test.

Table 2
Fluid intake during different time periods in very preterm infants born before (Before group, born in 2018) and after (After group, born in 2020) implementation of a nutritional care bundle. Data are presented as median and IQR.

Time periods	Before group (2018)		After group (2020)	
Total fluid, mL/kg/d	Median	IQR	Median	IQR
DOL 1–4	143.5 (n = 79)	136.0–153.5	124.0 (n = 70)	118.4–132.0
DOL 1–14	144.6 (n = 73)	138.8–155.6	143.9 (n = 64)	138.3–147.7
Parenteral fluid, mL/kg/d				
DOL 1–4	132.8 (n = 79)	123.0–143.3	98.4 (n = 70)	85.9–112.8
DOL 1–14	97.2 (n = 73)	54.0–142.2	50.2 (n = 64)	29.4–80.0
Enteral fluid, mL/kg/d				
DOL 1–4	7.5 (n = 79)	1.8–18.8	21.1 (n = 70)	7.7–41.3
DOL 1–14	48.3 (n = 73)	10.8–83.2	92.2 (n = 64)	64.6–113.7

DOL; Day of life.
IQR; Interquartile range presented as 25th – 75th percentiles.

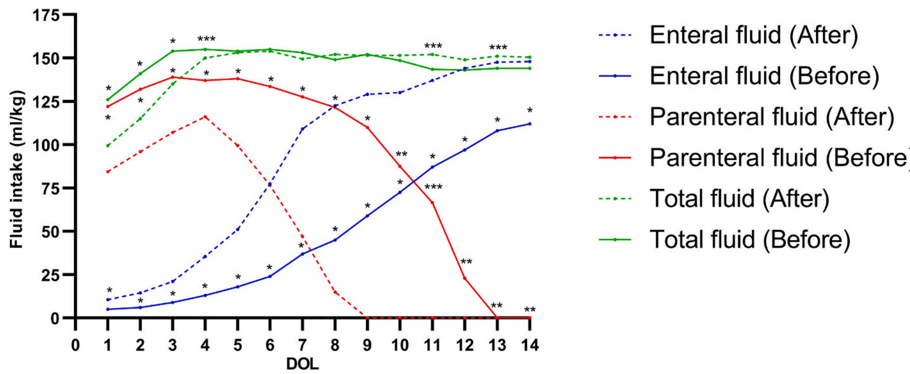

Fig. 2. Total, parenteral and enteral fluid intakes during days of life (DOL) 1 to 14 in very preterm infants born before and after implementation of a nutritional bundle of care. * P < 0.05. ** P < 0.01. *** P < 0.001.

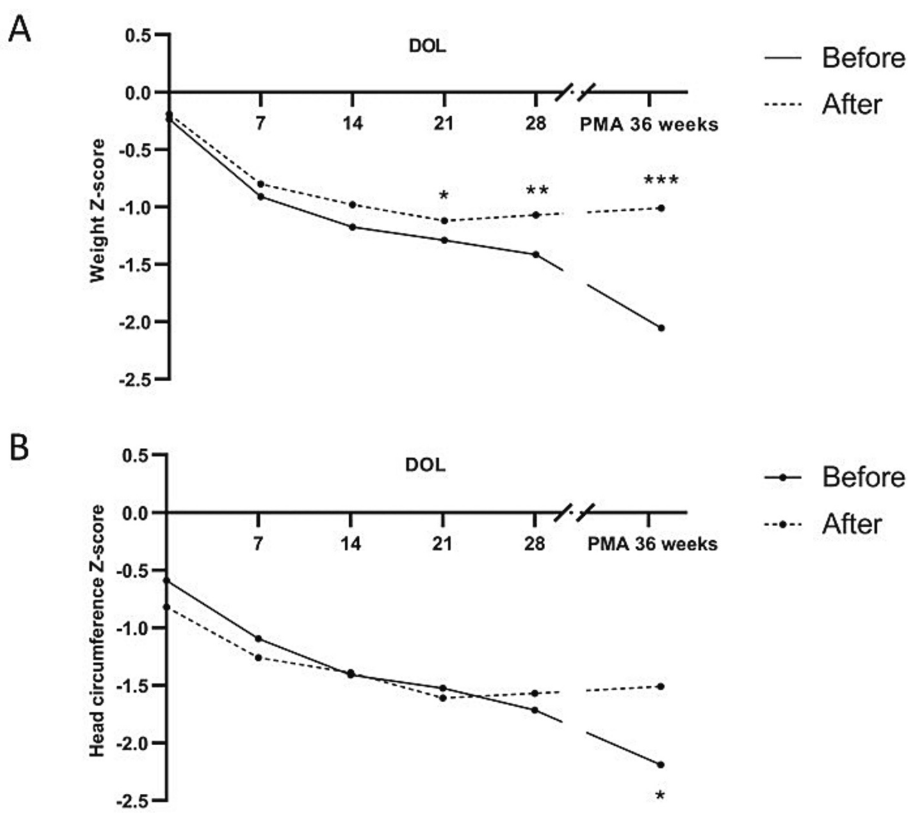

Fig. 3. Weight (A) and head circumference (B) z-scores during admission period in very preterm infants born before and after implementation of a nutritional bundle of care. * P < 0.05 ** P < 0.01 *** P < 0.001.

onwards. Compared to the BG, the AG had significantly higher weight z-scores from DOL 21 and onwards. Furthermore, the AG had significantly higher head circumference z-scores at 36 weeks PMA compared to the BG. Similarly, the AG had significantly higher mean±SD length z-score at 36 weeks PMA compared to the BG (−1.82±0.85 vs. -2.37±1.11, $P = 0.016$, Independent Samples *t*-test). Infants included in growth outcome analyses did not significantly differ in their baseline characteristics from infants included in the original study groups.

3.3. Morbidity

When analyzing all included infants in each group, a significant decrease in the rate of treatment-requiring PDA was noted between the groups, Table 3. More infants in the AG ($n = 7$) were treated with insulin compared with the BG ($n = 1$). No significant differences were found between the groups regarding treatment with inotropes, postnatal corticosteroids, or mechanical ventilation (Table 3). Furthermore, there were no significant differences between the groups regarding treatment with surfactant, number of treatment days with antibiotics or the occurrence of sepsis (data not shown).

4. Discussion

In this before-and-after study of a contemporary cohort of premature infants born before 32 gestational weeks, the implementation of a nutritional care bundle was associated with a significant decrease in fluid intake, improved postnatal growth, and decreased rates of treatment-requiring PDA.

In both groups, birth weight was used for fluid calculations until current weight exceeded birth weight; then current weight was used.

Table 3
Patent ductus arteriosus and complication treatments in very preterm infants born before (Before group, born in 2018) and after (After group, born in 2020) implementation of a nutritional care bundle.

	Before group, N = 79		After group, N = 70		P [a]
Morbidity	n	%	n	%	
Patent ductus arteriosus					
Pharmacological treatment	21	26.6	4	5.7	<0.001
Surgical ligation	3	3.8	0	0	0.248
Treatments					
Inotropes	6	7.6	3	4.3	0.502
Corticosteroids	12	15.2	4	5.7	0.070
Insulin	1	1.3	7	10	0.026
Mechanical ventilation	21	26.6	13	18.6	0.328

However, in the BG (infants born during 2018), fluid intake was calculated by the attending physician. In the AG (infants born during 2020), a software-based nutrition calculation system was used to calculate fluids allowing an overview regarding recommended fluid and nutrient intake in relation to weight and gestational age according to international guidelines [9,13]. The infants in the AG received significantly lower total volumes of fluids during the first 4 DOL compared to the infants in the BG. This decrease in volume may be attributed to the changes in parenteral nutrition solution used, from a standard solution to a highly concentrated one. It also reflects the decrease of target total daily volume intake as a part of the implementation of the nutritional care bundle, following the recommended guidelines for fluid intake and parenteral nutrition [23]. Our study showed that infants in the AG had significantly lower parenteral fluid volumes and higher enteral fluid volumes during the first 14 DOL compared to the infants in the BG. During the first 14 DOL, a greater number of infants in the AG achieved total enteral feedings compared to the infants in the BG (72.9 % vs. 51.9 %). Similar changes in total fluid intake were observed in a study by Westin et al. following the implementation of several nutritional care practices for extremely preterm infants born in Sweden between 2004 and 2011 [20]. This demonstrates that fluid and nutrition administered in adequate quantity might lead to shorter time with parenteral nutrition. Our results are in line with the data presented by Oczujda et al. who demonstrated that the use of a nutrition calculation software program is an important tool in achieving adequate parenteral fluid and nutrition supply [24]. Using such software in a clinical setting makes it easier to respond to changes in volume (e.g., due to enteral intolerance or the addition of medications) and to adjust the dosage according to the total volume of fluid the infant requires throughout the day. In contrary to our results, Späth et al. showed no difference in the total amount of administered fluids between groups of very low birth weight infants that received either a pharmacy-prepared parenteral nutrition solution or a commercial concentrated parenteral solution during the first week of life [6]. However, Späth et al. used the same software program in both groups to calculate daily fluid and nutrient intake, ensuring compliance with current nutritional guidelines during the NICU stay in both study groups. This might suggest that not only the parenteral nutrition solution in use is of importance, but also the daily use of automatized intake calculations and cross-check with current recommendations. A similar study including VPT infants concluded that a nutritional calculation program made it possible to offer nutrition that better complied with established guidelines [19].

The weekly multidisciplinary nutrition rounds included in our bundle of care allowed for regular revisions and adjustment of nutritional intake based on infant growth and health status. This individualized approach was associated with fewer negative growth outcomes in favor of the infants in the AG. In our study, the infants in the AG had significantly better total growth in weight, head circumference and length z-scores throughout the study period (from birth to 36 weeks PMA) compared to the infants in the BG. The weight outcomes observed are consistent with previous studies that have shown an increase in weight change from birth to 36 weeks PMA in relation to changes in nutritional regimens [6,25]. In our study, the AG had significantly higher weight z-scores from DOL 21 and onwards compared to the BG.

Although this is an observational study with limitations regarding causality, our findings are supported by previous studies. Early nutritional intervention and its impact on head circumference growth has been shown in the SCAMP trial by Morgan et al. where preterm infants who received a concentrated parenteral nutrition solution showed increased head circumference growth at postnatal day 28 compared to the control group [5]. Differences between the groups were still apparent at 36 weeks PMA. In our study, infants in the AG had significantly less negative length z-score compared to the BG at 36 weeks PMA. A similar observation was done by Späth et al. where infants who received a concentrated parenteral solution showed improved length gain from birth to 36 weeks PMA compared to infants who received a standard parenteral solution [6].

A recent publication showed that a standardized feeding protocol for preterm infants (<29 gestational age), which included close assessment of nutritional intake, was associated with growth rates that were close to the recommended target [26]. However, since nutritional data for the BG was impossible to obtain in our study, we can only speculate that the observed differences between the groups may be attributed to an overall improvement in energy and nutrient intake to meet the requirements for VPT infants.

In the BG, 15.2 % of the infants received postnatal corticosteroids compared to 5.7 % in the AG (Table 3). This difference may partially explain the growth disparity between the two groups. However, there were no significant differences between the groups at baseline and adjusting for postnatal corticosteroid treatment did not affect the results (data not shown).

An important issue is the occurrence of PDA in relation to adherence to the fluid regimen [9,13]. Stephens et al. showed that high fluid intake (>170 mL/kg/d) during the first postnatal days was associated with increased risk of PDA [27]. In a Cochrane review conducted by Bell and Acarregui, the authors concluded that by carefully limiting total fluid intake to meet physiologic needs without causing significant dehydration should reduce the risk of PDA [17]. In our study, there was a reduction in the incidence of treatment-requiring PDA in parallel with the reduction in fluid volume administered between groups.

There were significantly more infants that received insulin treatment in the AG (10 %) than in the BG (1.3 %). This might be a reflection of the higher frequency of hyperglycemia found. As previously presented, baseline characteristics did not differ between the groups which might suggest that this difference is due in part to the change in parenteral nutrition solution with a possible increased carbohydrate intake. However, it was previously shown by Zamir et al. that parenteral nutrition does not affect hyperglycemia in preterm infants to a substantial extent [28]. Furthermore, it was not possible for us to compare the carbohydrate intake between the groups (see study limitations described below).

The strengths of this study are the contemporary study population of VPT infants and the use of a 1-year "wash-out" period (2019) while the nutritional care bundle in the NICU was fully implemented. For the AG, data collection was done in a prospective manner using a software-based nutrition calculation system. Another strength is the detailed data regarding fluid intakes during the first 14 DOL. Study limitations include the retrospective data collection for the BG. The NICU did not use electronic records during 2018 and it was impossible to obtain data regarding daily intakes of energy and nutrients from hospital records. Further on, the relatively small sample size makes it difficult to detect significant changes in rates of perinatal morbidity as well as affects its generalizability. No long-term follow-up data was available for this work and thus long-term effects could not be determined. Due to the study design, it is difficult to draw conclusions regarding causality and it is possible that other factors and interactions may have influenced the results.

The results of this study are clinically relevant because they suggest that implementation of a relatively simple nutrition care bundle was associated with a significant change in the z-score for weight, head circumference, and length at 36 weeks PMA. A change to a concentrated parenteral nutritional solution, targeted fortification of breast milk, daily use of a software-based nutrition calculation system, and weekly nutrition rounds in the NICU, were associated with improved anthropometric values in favor to the infants in the AG. These interventions maintained adequate fluid intakes and enabled shorter time to full enteral feedings without increasing morbidity rates. The present study replicates the introduction process described in the studies by Späth et al. [6] and Wackernagel et al. [19] and adds evidence for the positive effects of implementing a nutritional care bundle in the setting of a modern NICU.

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CRediT authorship contribution statement

Jiří Dušek: Conceptualization, Data curation, Investigation, Methodology, Resources, Writing – original draft. **Elisabeth Stoltz Sjöström:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Itay Nilsson Zamir:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors have no conflict of interest relevant to this article to disclose.

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