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Improved nutrition for extremely preterm infants -a population based observational study

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ABSTRACT

Background and Aims: Extremely preterm (EPT) infants are at high risk for malnutrition due to immaturity and medical complications and they often accumulate nutritional deficits and experience growth faltering during treatment at neonatal intensive care units (NICUs). Enhanced intake of energy and protein during the first weeks of life improves weight gain and head circumference growth. The optimal nutritional strategy for these infants' health and long-term development remains unknown. Nutritional regimens have been identified as a potential area for improvement in Swedish NICUs. The aim of this study was to evaluate changes in nutritional intake over time during the first 56 postnatal days in EPT (<27 gestational weeks; n=316) infants, who were treated in NICUs during 2004-2011 in Stockholm, using a population-based study approach.

Methods: Several different nutritional interventions were implemented over the 8-year period. Nutrition and growth data were obtained retrospectively from hospital records. All intakes of enteral and parenteral nutrients were retrieved daily during the first 28 postnatal days and on days 35, 42, 49 and 56.

Results: Energy intake (median) increased from 77 kcal/kg/d during the 2004-2005 period to 98 kcal/kg/d during the 2010-2011 period on days 4-6. Median protein intake increased from 2.4 g/kg/d during 2004-2005 to 3.6 g/kg/d during 2010-2011. Energy and protein intake during postnatal days 0-6 increased continuously over the 8 years and protein intake increased during all 56 postnatal days. Full enteral feeds were reached earlier and the proportion of enteral feeds during the first week was higher during 2008-2009 compared to all other years. A significant improvement in growth was primarily noted by comparing the 2004-2005 period

to subsequent years.

Conclusions: Neonatal nutrition improved significantly in Stockholm from 2004 to 2011. Above all, parenteral nutrition was initiated more promptly during the first week and was provided at higher quantities. However, many of the EPT infants born during the later years still did not reach the recommended macronutrient intake levels. A significant weight gain improvement was observed between 2004-2005 and 2006-2011.

Key words:

Enteral nutrition, Energy, Parenteral Nutrition, Preterm infant, Protein

Abbreviations

BW, Birth weight; CI, Confidence interval; DHM, Donor human milk; EN, Enteral nutrition; EPT, Extremely preterm; GA, Gestational age; HMF, Human milk fortifier; MOM, Mothers' own milk; NEC; Necrotising enterocolitis; NICU, Neonatal intensive care unit; PN, Parenteral nutrition; SDS, Standard deviation scores; SNQ, Swedish national quality register.

INTRODUCTION

Improved survival among the most premature infants has been noted during the past decades (1, 2), but concerns about morbidity and later disability in these infants remain (3, 4).

Extremely preterm infants (EPT, <27 weeks' gestational age) are at great risk for feeding difficulties due to gut immaturity and medical complications (5). As a result, these infants commonly accumulate nutritional deficits and experience extrauterine growth restriction while being treated in neonatal intensive care units (NICUs) (6-8).

During recent years, an increasing number of studies have focused on both enteral and parenteral neonatal nutrition (9, 10). Early parenteral administration of lipids and amino acids are well tolerated by preterm infants with a birth weight of ≤ 1500 grams (11). Enhanced intake of energy and protein during the first weeks of life also promote better weight gain and head circumference (HC) growth (12, 13). By optimising nutritional regimens in the NICU during the first weeks of life, it may be possible to meet nutritional requirements and prevent postnatal growth restriction in EPT infants (14). Premature infants who are fed their mothers' own milk (MOM) tolerate full enteral feeds earlier and have a reduced risk of developing necrotising enterocolitis (NEC) than those fed formula (15, 16). Moreover, the benefit of using human milk fortifiers (HMF) is associated with short-term outcomes such as improved postnatal growth (17).

Practice guidelines have recently been updated, building on the evidence gathered regarding nutritional management of preterm infants (18, 19). However, the optimal nutritional strategy for health and long-term development is not yet known, and implementing continuously updated new knowledge in a clinical setting is a multi-layered task (20). Early nutritional

practices have been identified as an area with potential for improvement in Swedish NICUs (21, 22).

The aim of the present study was to describe changes in nutritional regimens of EPT infants during an 8-year period from 2004 to 2011. Infants were treated in NICUs in Stockholm, Sweden and differences in fluid, energy and macronutrient intake and postnatal growth during the first 56 postnatal days were evaluated.

METHODS

Study population

All infants with a gestational age of 22 0/7 weeks to 26 6/7 weeks, who were born in Sweden between April 1, 2004 and March 31, 2007, were included in the Extremely Preterm Infants in Sweden Study (EXPRESS). Detailed data on cohort characteristics, neonatal morbidity and infant mortality have previously been reported (2, 4). For the current study, we included infants from the EXPRESS cohort who were born and treated in Stockholm, as well as all infants born with a gestational age of 22 0/7 weeks to 26 6/7 weeks, who were treated in Stockholm between January 1, 2008 and December 31, 2011. All infants who survived >24 hours after birth were included (n=348).

We excluded infants with major congenital or chromosomal anomalies. Infants reported to have undergone abdominal surgery were excluded after surgery due to expected interference with enteral nutritional absorption. Infants with missing or incomplete nutritional data were also excluded. Infants with hydrocephalus were included in the analyses of given nutrition, but excluded from the illustration of growth due to expected non-physiological growth.

Infants who died were included in the analyses until their death. The final study population consisted of 316 EPT infants (Supplementary Figure).

Data collection

Nutritional intake and anthropometric measurements were retrospectively obtained from hospital records by the first authors and trained local staff. Daily nutritional intake was obtained from birth (day 0) to postnatal day 27 and once a week (day 35, 42, etc.) thereafter until postnatal day 56. Detailed information was obtained from hospital records for actual intake of all nutritional parenteral and enteral fluids including amino acids, lipids, glucose infusions, added electrolytes, MOM, donor human milk (DHM), type of HMF, and of vitamin and mineral supplements.

Nutrition was assessed as both combined and separate parenteral and enteral intakes of energy (kcal/kg/d), amino acids/ protein, lipids/fat, and carbohydrates (g/kg/d). Fat was also assessed as part of total energy content (E%) and amino acids were counted as proteins. Henceforth, amino acids and lipids are referred to as protein and fat, respectively. Nutrient intake from nutritional products was calculated using information from manufacturers. Detailed compositions of prescribed parenteral nutrition for each infant were used. Breast milk samples, MOM, and DHM were analysed for energy and macronutrient content using mid-infrared spectrophotometry analysis (MilkoScan 4000) at Eurofins Steins Laboratory AB, Jönköping, Sweden. Local guidelines at Karolinska University Hospital recommended analysis of MOM every other week from 1 to 2 weeks postnatal age. For MOM not analysed, macronutrient content was assumed to equal the average content of analysed breast milk samples. If MOM production was suboptimal, DHM was given, until the infant reached a postnatal age of at least 32 to 35 weeks. During the study period, DHM was pooled, meaning

that breast milk samples from four different donors were used. Full enteral feeding was defined as the first day of enteral intake of ≥ 150 ml/kg/d or no parenteral nutrition according to Cormack et al (23).

Nutritional data was considered unreliable if infants were transferred to home care ($n = 3$) or if infants received unaccountable amounts of enteral nutrition due to breast feeding ($n = 8$). Anthropometric measurements of weight, length and HC were obtained from growth charts. All data were entered and stored using a computer-based tool (Nutrium™) that was especially designed for neonatal care. The first authors continuously controlled and validated data against original hospital records throughout the data collection period. Perinatal data was prospectively gathered in the Swedish Neonatal Quality (SNQ) register.

Changes in nutrition

Several aspects of the nutritional practices in the NICUs were altered over time during the study period (Figure 1).

Parenteral nutrition

Changes in parenteral nutrition recommendations including increment advancements in the recommended amount of protein and fat during the study period are described in Figure 1 and in Supplementary Table.

A standardized, extemporaneously prepared parenteral nutrition “Start-up” was introduced in 2009 to facilitate the early start of parenteral infusion including protein (Figure 1). During 2009, the parenteral fat component was changed from only poly-unsaturated fatty acids (soy oil) to a mixture of mostly mono-unsaturated fatty acids (80% olive oil and 20% soy oil).

Enteral nutrition

Detailed information regarding changes in enteral nutrition and the recommended amount of protein and fat as well as changes in the advancements of enteral feeds during the study period are described in the Supplementary Table.

Standard practice over time (from 2004-2011) was to use MOM or, if not available, DHM. Minimal enteral feeding at 10 ml/kg/d from day of birth, with an increase of 10 ml/kg/d, was recommended in local guidelines in 2006 and were based, on a continuous feeding study by Dsilna et al (24). Amounts of HMF were advanced more rapidly during the latter years. Target fortification based on analysed MOM, and DHM was used throughout the study period. The HMF containing whole protein (Pre Semp, Semper AB, Sweden) was replaced in 2006 with a HMF based on extensively hydrolysed protein (FM 85[®], Nestlé, Switzerland). To optimise energy needs, HMF containing 50% long chain fatty acids and medium chain fatty acids emulsions (Calogen[®] Neutral and Liquigen[®], Nutricia Nordica AB, The Netherlands) were used. HMF containing both fat and carbohydrate (Duocal Neutral, Nutricia Nordica AB, The Netherlands) was used to prevent fat intake exceeding the maximum recommendation of 55 E%. From 2006, formula (Nutramigen[®], Mead Johnson Nutrition, The Netherlands and Althera[®], Nestlé, Switzerland) without cow's milk protein was used as a fortifier when feed intolerance was observed.

Changes in clinical practice

Implementing revised local guidelines required changes in practices and educational processes within the Stockholm NICUs, which have evolved continuously over time (Figure 1). Parenteral solutions have been individually prescribed on a daily basis by the on-call neonatologist who was informed and educated on the protocol changes over time. Since the

late 1990's, the individual enteral nutritional needs of preterm infants in the tertiary care unit were calculated, according to breast milk analyses by the neonatal dietitian. From late 2007, a full time neonatal dietitian was employed at three of the four NICUs in Stockholm and applied the target fortification. A web-based program for nutrition and growth (Nutrium™) facilitating nutritional calculations and an education program regarding neonatal nutrition for the ward staff were introduced in these units during the same year. Designated education of nutrition assistants working in the ward kitchen was also set up in 2007. At the end of 2010, a supplemental computerized ICU system (Centricity Critical Care Clinisoft, GE Healthcare) was introduced, registering all parental fluids and medications and enteral intakes including fortification of MOM and DHM. This facilitated the supervision of the nutritional process in two of the four NICUs in Stockholm.

Statistical analyses

The 8-year time-period was divided into four 2-year periods when analysing the data. All analyses were performed using Stata/IC 14.2 software (StataCorp LP, College Station, Texas, USA) and IBM SPSS Statistics version 20 or later (IBM Corp., Armonk, N.Y., USA). Due to the aim to describe the population and the nutrition given as illustratively as possible and because of the non-normal distribution of some of the variables, all numerical data are presented using the median and 10th to 90th percentile range. Comparisons of clinical variables between groups were performed using chi-square test for categorical data. Comparisons of numerical measures were performed using quantile regression with bootstrapped confidence intervals (25). Preterm growth charts by Fenton et al (26) were used to calculate standard deviation scores (SDS), regarding weight, length and HC. The definition of small for gestational age (SGA) was weight below the 10th percentile. Growth data is illustrated in mean values using mixed effects model with restricted cubic splines (27, 28). A p-value < 0.05 was considered as statistically significant.

Ethical approvals

This study was approved by the regional ethical review boards (Lund 2004-42, amendments 2006-201 and 2008-138; Stockholm 2007/1613-31, amendment 2013/265-32).

RESULTS

Characteristics of the 316 infants included in the analyses are presented in Table 1. During the first 4-56 days of life, 35 infants died. Within the first 56 postnatal days, 14 infants were transferred to hospitals in other regions and 16 infants underwent abdominal surgery (Supplementary Figure).

Median birth weight (BW) was significantly higher, and days on mechanical ventilation were significantly lower, during the 2006-2007 period compared to all other years (Table 1). There was no significant difference in gestational age (GA) at birth between the years analysed, but the proportion of infants born in gestational week 26 was higher during the 2008-2009 period compared to 2010-2011 period. No significant differences were noted regarding BW-SDS or APGAR scores.

Intakes of energy, macronutrients, and fluids are shown in Table 2. The differences between the years 2004-2005 and 2010-2011 are stated with 95% CI.

Energy intakes during days 0-3 and days 4-6 were higher during the 2010-2011 period compared to all previous years. Energy intake from days 4-6 was significantly increased during every 2-year period. Among the infants receiving the least amount of energy in the 10th percentile, energy intake during the first 56 postnatal days increased by 17.6 kcal/kg/d (95% CI: 7.9-27.3) from the 2004-2005 period, compared to the 2010-2011 period ($p < 0.001$).

Protein intake increased continuously over the years. The most noticeable increase was during the first days of life. Protein intake during days 0-3, 4-6, and 7-27 were higher during the 2010-2011 period compared to all previous years. Fat intake increased over every 2-year period during days 0-3, and during days 4-6 over the first 4 years. Carbohydrate intake was not increased during the first days of life.

An increase in total fluid intake was observed between the first and subsequent year periods. Enteral fluid intake in relation to total fluid intake is illustrated in Figure 2. During postnatal days 0-6, the proportion of enteral intake was greater during the 2008-2009 period than all other periods (median 15.3% during 2008-2009 vs 8.5% during 2010-2011; difference 6.7% [95% CI: 2.2-11.2], $p<0.01$).

There was no consistent time trend from 2004-2011 regarding advancement of enteral feeds. Among infants not undergoing abdominal surgery, the median (10th-90th percentile) time to full enteral feeds was significantly shorter during a single 2-year period (2008-2009), at 15 (8-34) days compared to all other 2-year periods: 23.5 (12-51) days from 2004-2005; 21 (12-36) days from 2006-2007; and 23 (10-41) days in from 2010-2011. Infants receiving more than 50% of their fluids as enteral feeds, but not full enteral feeds, during days 7-27 had a higher total energy intake during the 2010-2011 period compared to all previous years. This difference was due to a higher energy intake from parenteral feeds, and no longer significant when more than 75% of the total fluids were provided as enteral feeds.

The enteral energy intake during days 7-27 for infants receiving full enteral feeds did not differ significantly over the years, in the median or 10th-90th percentiles. The enteral protein content was increased and significantly higher during 2010-2011 compared to the previous

years. Median (10th-90th percentile) protein intake during days 7-27, when on full enteral feeds, was 3.0 g/kg/d (2.5-3.6) during 2004-2005; 3.0 g/kg/d (2.3-3.7) during 2006-2007; 3.3 g/kg/d (2.7 to 3.8) during 2008-2009 and 3.6 g/kg/d (2.7-3.9) during 2010-2011. Enteral E% of fat when infants received full enteral nutrition during days 7-27 was higher during 2004-2007, with a median of 51.7% (46.6-57.8, 10th-90th percentile) versus 2008-2011, with a median of 47.0% (41.2-51.3, 10th-90th percentile).

Growth is illustrated in Figure 3 as changes in mean SDS for weight, length and HC during the first 56 postnatal days. Postnatal growth restriction was common during the entire period studied. A significant improvement in weight gain was primarily noted by comparing the period during 2004-2005 to subsequent years. The difference was 0.3 SDS (95% CI: 0.1-0.5, $p<0.001$) in weight at postnatal day 7, and this difference was sustained at day 56 at 0.4 SDS (95% CI: 0.2-0.7, $p<0.001$). Length and HC were not measured as frequent as weight and significant differences were noted only during later weeks. The difference between the period during 2004-2005 and subsequent years was 0.5 SDS (95% CI: 0.2-0.8, $p<0.001$) in length and 0.5 SDS (95% CI: 0.2-0.8, $p<0.001$) in HC at postnatal day 56.

DISCUSSION

Our findings demonstrate improved energy and macronutrient intake in EPT infants in Stockholm over the period from 2004-2011. Even though enteral nutrition was not provided to the same extent during 2010-2011 compared to 2008-2009 the total amount of energy and macronutrients given were still at a high level. Our results illustrate the implementation of new knowledge that has emerged in the field of neonatal nutrition in the NICUs in Stockholm. The changes in nutritional interventions were implemented over multiple years and we cannot identify which factors contributed to which effects. Enhanced focus, education of personnel,

and facilitating software had a combined impact leading to increased nutritional intake. Nonetheless, at the end of this study a considerable number of infants did not achieve the amount of energy and macronutrients currently recommended in Sweden (29). In this study, we did not analyse intake related to outcome adjusted on the individual level. The aim of this study was to describe changes in nutritional regimens and evaluate differences in nutritional intake.

The major improvements in energy, protein, and fat intake during postnatal days 0-6, could be explained by a more aggressive approach regarding early parenteral nutrition.

Recommendations for minimal energy requirements of 85-95 kcal/kg/d to parentally fed infants (18) were met on days 4-6 by almost 90% of the infants born during 2010-2011.

Introduction of higher amounts of protein and fat as soon as possible after birth and a swifter escalation of the given amounts was promoted in local guidelines 2006 and 2011. Van Goudoever et al concluded that an initial intake of 2.0-2.5 g protein/kg/d was safe (18). In this study, as reflected by the 10th percentile during 2010-2011, 90% of the infants had protein intakes on postnatal days 0-3 of more than 2.0 g/kg/d. The introduction of “Start-up” in 2009 made initiation of protein supply more easily available on nights, weekends, or holidays when individually ordered parenteral nutrition could not be prepared. More than half of the infants in this study reached the recommended intake of 3.5 g/kg/d protein, according to recommendations stipulated by Koletzko et al (18), within 6 postnatal days during 2010-2011 period, but only 10% of the infants achieved this goal during the years 2004-2007. A recommended initial intake of 2.0 g/kg/d of fat (18) was achieved by more than half of the infants on days 0-3 during the years 2008-2011. Intake of energy and fat in this cohort were highest during the 2008-2009 period from postnatal days 7-13 and 14-20, respectively, reflecting a higher proportion of enteral intake. The nutrient content in enteral feeds has been

altered over the years to include more protein and less fat, with no difference in total energy.

The importance of infrastructure as well as designated ward staff for improved adherence to nutritional guidelines has previously been described (30). The effect of computer software to facilitate prescriptions and documentation of nutritional intake has been demonstrated by Wackernagel et al (31). In 2003, Kuzma-O'Reilly et al showed, among other results, an improved time to reach full enteral nutrition and more consistent nutritional support after implementation of potentially better practices in the NICU (20). In a group of very low birth weight infants, Rochow et al found that infants receiving higher amounts of parenteral protein and fat, and with daily adjustment of enteral feeding, attained full enteral feeds 5 days earlier than a control group, all due to a standard nutritional schedule (32). In our study, we demonstrate a bundle of interventions leading to increased nutritional intake. Full enteral feeds were obtained sooner during 2008-2009, demonstrating an improvement from the 2004-2005 period. However, in 2010-2011, the median time to full enteral feeds was almost the same as in 2004-2005, although the distribution was shifted as reflected by the shorter times for full enteral feeds at the 10th and 90th percentiles. There was no significant difference in GA between the later year-group periods at birth except a higher proportion of infants born at gestational week 26 during 2008-2009. This difference was accentuated after examining the surviving infants included in the nutrition analysis. The distribution of GAs might partly explain the different feeding patterns during the later years.

Achieving adequate energy intake still constitutes a challenge during the transition phase from parenteral to enteral nutrition. Timing of the introduction of HMF and lack of consensus on indications for withholding feeds could be an important reason for difficulties in reaching target intakes. Use of breast milk-based fortifiers together with advancement of daily

increments > 24 mL/kg/d has been suggested to prevent the energy slope during the transition phase from parenteral to enteral feeds (13, 33).

Studies have shown that improved nutritional intake result in better postnatal growth in preterm infants (34, 35). Saenz de Pipaon et al demonstrated the difficulty in meeting intrauterine growth rates, despite achieving energy and protein intakes close to the recommended target levels (36). Our study presents improved growth compared to the earliest period during 2004-2005, but infants still did not reach the intrauterine growth curve, in later years. Compared to the growth trajectories for EPT infants suggested by Rochow et al (37), during the years of 2006-2011, infants in our study showed similar postnatal growth patterns in weight. The relevance of differences in weight gain during the first weeks of life and in later catch-up growth phases could be of importance, but need to be evaluated in detail. The improved growth in length and HC should be interpreted with caution due to sparse measurements. Further analysis of possible correlations between nutritional intake, growth, and morbidity in relation to GA and BW in this cohort is planned.

The major strength of this study is the detailed data presented regarding nutrient intake including the content of parenteral solutions and analyses of breast milk administered to a large number of EPT infants during an 8-year period of evolving neonatal nutritional regimens. A limitation is the retrospective design and the multitude of implemented actions during the study period making a strict interventional comparison impossible. Nutritional practices have most likely continued to improve after the termination of this study.

We conclude that there has been a significant improvement in neonatal nutrition and growth in Stockholm during the study period coinciding with an introduction of a nutritional bundle

of care. Parenteral nutrition is initiated earlier, with higher amounts of protein and fat, resulting in the most prominent differences in intake the first week of life. Despite these efforts, many of the EPT infants did not achieve the recommended macronutrient intake towards the end of the study period and there is still potential to continue improving neonatal care in our NICUs.

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Statement of authorship

VW and SK contributed equally to this work. VW, SK, MD and BH designed the study. SK, VW and ESS were responsible for nutritional and growth data acquisition. VW and SK drafted the initial manuscript and performed statistical analyses. VW, SK, MD, MV, BH, and ESS analysed and interpreted data; participated in writing the manuscript; reviewed and revised the scientific content of the manuscript; and gave final approval of the manuscript that was submitted for publication.

Conflicts of Interest, Statement and Funding Sources

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Information of tables and figures

Figure 1

Action bundles of nutritional changes in Stockholm 2004 to 2011

Figure 2
Median intakes of enteral fluids in relation to total fluid intake the first 28 postnatal days by year-group.

Figure 3
Growth the first 56 postnatal days by year-group expressed as shift in mean standard deviation score (SDS) (26). (A) Weight, (B) Length (C) Head Circumference
300 infants were included in figure of weight; 294 infants in figure of length, and 295 infants in figure of head circumference. Grey bars denote 95% CI.