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Title page

Stoma closure improves head circumference growth in very preterm infants after necrotizing enterocolitis

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Abstract:

Introduction: Very preterm infants (VPI) surgically treated for necrotizing enterocolitis (NEC) are at risk of growth retardation. The aim of this study was to demonstrate and compare growth during the first 6 years of life in VPI with stoma after NEC-surgery with VPI without NEC-surgery.

Materials and Methods: We included all VPI surgically treated due to NEC at Odense University Hospital from August 1st 2004 to July 31st 2008. Outcome on growth was compared to a group of VPI without NEC. The VPI with NEC were identified searching the local database using the ICD-10 diagnosis of NEC (DP77.9). Data on growth was collected from medical files and if not present, the parents reported the data.

Results: Nineteen VPI, surgically treated due to NEC, survived to 6 years of age. Median gestational age was 28 weeks + 3 days (24+5 to 31+3). Median age at NEC-surgery and stoma formation was 2.3 weeks (0.1 to 6.3) and median age at stoma closure was corrected age (CA) 2.5 months (postmenstrual age 36 weeks to CA 6.7 months).

Compared to the non-NEC group VPI with NEC and stoma demonstrated poor growth, especially in head circumference (HC) with no increase in growth velocity before time of stoma closure between 2.5- and 3-month CA.

Conclusions: Our findings demonstrate poor growth in very preterm infants after NEC surgery and improved HC growth after stoma closure.

Key words: very preterm infants, necrotizing enterocolitis, stoma closure, nutrition and growth

Introduction:

Necrotizing enterocolitis (NEC) is one of the most common conditions that need surgical treatment in infancy, occurring primarily in very preterm infants (VPI) (GA<32 weeks). The risk of developing NEC increases with lower birth weight (BW) and lower gestational age (GA) and the mortality is high[1]. When advanced disease is present the only option for survival is surgical treatment which leads to a number of complications such as temporary enterostomy with or without short bowel syndrome (SBS), malabsorption and poor growth.[2,3] The optimal time for stoma closure is discussed and there is no consensus regarding the best time – during, or several months after initial surgery.[4,5,6] As numbers of NEC survivors are increasing, it is important to clarify outcome on e.g. growth later in life among these children.[7] There have been conflicting findings in the literature with a tendency towards growth retardation in children with surgical treated NEC, but most studies have a short follow-up time limited to the first years of life. Studies have shown that poor growth and small head circumferences (HC) during early childhood is associated with poor neurological outcome.[8,9,10,11]

The aim of this study was to demonstrate and compare growth during the first 6 years of life in a group of VPI after NEC-surgery with a group of healthy VPI.

Material and Methods:

Study design and population: We included all VPI diagnosed with NEC and treated with surgery from August 1st, 2004 to July 31st, 2008 (group B). The infants were recruited from 4 neonatal units in Denmark (Odense, Kolding, Skejby and Holbaek). The infants were identified by searching the database (Neobasen) using the ICD-10 diagnosis of NEC. (DP77.9) VPI, who were not surgically treated for NEC or had an explorative laparotomy and

enterostomy for other reasons than NEC, including children with spontaneous intestinal perforation (SIP)/focal intestinal perforation (FIP), were excluded. Growth data on weight, length and HC were collected from their medical files until the children were 36 months old. Growth data at 6 years were also collected from their medical file if present. If not, the parents were asked to report the data by mail or phone. Other characteristics such as gestational age (GA), birth weight (BW), small for gestational age (SGA), or non-SGA, single- or multiple-birth, age at surgery, length of the remaining bowel classified as more or less than 50 %, nutrition while having a stoma and age at stoma closure has been registered from medical files. Outcome on growth in group B were compared to growth data in VPI without NEC or any feeding-disabilities at discharge from the 4 neonatal units, included in a previous published prospective randomized controlled trial (RCT) evaluating the effect of fortified human breast milk post discharge on growth in VPI until 6 years of age.[12,13]

Ethical approval: Handling of data and registrations are approved by the Danish Data Protection Agency (in 2015; journal No. 15/20712). Ethical approval was not relevant in this study, but the original RCT used for comparison was approved July 1st, 2004 by the Danish National Committee on Biomedical Research Ethics (J.nr. VF20030208).

Statistical analyses: Data were analyzed using STATA (version 16). Wilcoxon rank-sum test or t-test was used for continuous variables and chi^2-test for categorical variables. Z-score or standard deviation score (SDS) was calculated as the difference between the actual weight/length/HC and the expected reference weight/length/HC divided with 1 standard deviation (SD) (ex: (BW – references BW / 1 SD). Growth references used for calculating z-scores for each gender were according to Niklasson and Albertsson-Wikland.[14] Mean z-scores were used to calculate change in z-score (delta z-score) from week 34 postmenstrual age (PMA) and until week 36 PMA, 40 PMA (=term), 2, 4, 6, 12, 24, 36 month and 6 years

corrected age. Being SGA was defined as a BW z-score below or equal to -2 SDS. Multiple logistic regression was used to evaluate factors (GA<28 weeks, gender, SGA, multiple birth and SBS, defined as loss of more than 50% of the small intestine),
possibly influencing delta z-scores comparing group B (NEC) with group A (breastfed post discharge) and group C (formula fed post discharge), respectively.

Results:

Twenty-five VPI were treated surgically due to NEC and 19 survived to 6 years of age (group B). Five infants with surgical NEC were diagnosed with SBS.
The groups for comparison consist of 215 infants; 102 breastfed at discharge and 113 formula-fed at discharge.[13] Infants with surgical NEC had a significant lower median GA and birth weight compared to the VPI without NEC. Thirty-two percent were small for gestational age (SGA) and 58% were multiple birth. Sixty-three percent were boys. There was no difference in the proportion of SGA, multiple birth or gender. (Table 1).
The characteristics of the infants with surgical NEC are shown in table 2 and 3. The median age at surgery and stoma formation was 2.3 (0.1 to 6.3) weeks and the median age at stoma closure was 2.5 months corrected age (CA) (postmenstrual age (PMA) 36+1 to CA 6.7 months). There was one outlier with GA 24+5 who had surgery at PMA 27+0 and stoma closure 40.1 weeks after initially surgery at 6.7 months CA. This infant was not diagnosed with SBS. Mean z-scores for all 3 groups from birth to 6 years of age and delta z-score for all 3 groups from PMA 34 weeks until 6 years of age are shown in figure 1. Infants in group A and C increased significantly more in HC z-score from 34 weeks PMA and until 36 PMA, 40 PMA, 2, 4- and 6-months CA compared to group B ($p \leq 0.03$). No significant differences were found at 12 months CA, 2, 3 and 6 years of age. There was a significant difference in weight delta z-score until 4 months CA comparing B with A ($p \leq 0.007$) and until 36 months CA

comparing B with C ($p \leq 0.03$). There was a significant difference in length from term to 4-month CA comparing B with A ($p \leq 0.03$) and until 6 months CA comparing B with C ($p \leq 0.02$).

Discussion:

It is not surprising that the infants with surgically treated NEC demonstrated increase in weight before time of stoma closure. It has been standard in our department to plan stoma closure when the VPI demonstrates an increase in weight. But focus has not been on head circumference growth prior to stoma closure, and surprisingly NEC VPI did not demonstrate increase in head circumference growth until after stoma closure.

Several studies have demonstrated an association between poor head growth during NICU admission and neurodevelopmental impairment at follow-up between 18-36 months CA, but also that the risk of neurodevelopmental impairment is reduced with increase in head growth velocity.[11,15] Both Walsh and Hintz demonstrate smaller head circumference and neurodevelopmental impairment in infants with NEC until 2 years, although Hintz only finds it significant in children who have been surgically threated for NEC in infancy.[16,10]

Among children with NEC, Rees et al. have included 10 studies in a meta-analyse with a median follow-up time of 20 months, where cognitive impairment among 369 NEC children in 7 studies were 36 % vs. 24 %, and psychomotor impairment were 35.1% vs. 23.2% among 328 NEC children in 5 studies.[17] Only 3 studies have looked at the neurodevelopmental outcomes in school aged children with NEC[1,9,18] but only one of them[9] measured head circumference and demonstrates a smaller head circumference for age (not significant, p-value 0.08) adjusted for other explanatory variables. But their data were based on parental questionnaires with a low response rate, with a tendency of NEC children with fewer complications to respond and the opposite for the children without NEC, which could have

caused bias. By 6 years of age, we do not find any significant difference in head circumference between our groups, but most of our data for head circumference at this age were also reported by the parents. All authors do find the tendency that the children with NEC are more likely to have neurodevelopmental impairment, though not significant.

There are by date no consensuses regarding the best time for stoma closure. A systematic review from 2012[5] based on only 5 studies including 1 prospective cohort study and 4 retrospective cohort studies found no difference in complication rates comparing early vs. late stoma closure defined by 8 weeks before or after initial stoma formation and a meta-analysis from 2017[19] reaches the same conclusion. Al-Hudhaif J et al.[6] is the only group of the above mentioned publications, that demonstrate significant more postoperative complication in infants with early stoma closure such as longer need for ventilator support and longer need for total parenteral nutrition, but it is a small study including only 10 patients with early stoma closure. Banerjee et al. later reaches the same conclusion in a cohort of 15 infants with early stoma closure vs. 21 with late stoma closure.[4] To our knowledge there are no studies comparing early vs. late stoma closure and effect on head circumference growth and neurodevelopmental delay as an outcome, but Rothstein[20] described 6 infants with NEC and ileostomy who all had serious fluid and electrolyte losses and developmental delay with recovery after stoma closure advocating for earlier stoma reversal.

Because of multiple complications to enterostomy several surgeons have chosen primary anastomosis after resection as first choice. Again, there are no randomized trials to support which technique should be preferred. A meta analyses from 2017 include 12 observational studies from the period of 1979-2010 that compare primary anastomosis vs. ostomy and find no significant difference in the risk of complications. Although they found primary anastomosis was associated with better survival, it could be due to the fact that surgeons prefer stoma formation in the most severely ill patients.[21] We have not found any studies

comparing head circumference or neurological outcome in VPI with NEC having either enterostomy or primary anastomosis. We are aware of the limitations in our study design, but because NEC only occur in a small subgroup of infants with an incidence varying from 5-12%[9] it is very difficult to set up a RCT with enough participants. It could have been relevant to look at the stoma level in group B, as we know that children with jejunostomy have a higher risk of malabsorption[22]. Unfortunately we do not have that data, but we have defined whether they have SBS or not. We do have a relatively large cohort and a large comparable group of healthy VPI. We also consider our growth data to be valid because all the growth data until at least 36 months are collected from the medical files where the measurements are done in a standardized way by a trained nurse or medical doctor.

Unfortunately, we only have the IQ-scores and other neurodevelopmental outcomes from the children in group A and C (will be published elsewhere) although it would have been of interesting to compare IQ-scores and neurodevelopmental outcome between groups.

Conclusion:

We have demonstrated that despite all attempts in optimizing nutrition in very preterm infants after NEC-surgery and stoma formation, the infants in our study did not show increase in head circumference growth velocity before stoma closure was performed. This finding might suggest early stoma closure or using primary anastomosis to improve head/brain growth and thereby probably minimize the risk of neurodevelopmental impairment later in life, but more research is needed using head circumference and not only weight growth as an outcome.

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Conflict of interest: The authors do not have any conflicts of interest

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Figure 1. Z-scores and delta z-scores for group A, B, C showing weight, length and head circumference (HC) from birth until 6 years of age.

Table 1. Characteristics of participants within groups.

	A (Human milk post discharge) (n=102)	B (NEC and stoma) (n=19)	C (Preterm formula post discharge) (n=113)	A+C vs. B P-value
GA at birth (weeks + days) median (min-max)	29+5 (24+1-32+0)	28+3 (24+5-31+3)	29+4 (25+1-32+0)	0.014
BW (g) median (min-max)	1260 (548-2255)	1012 (668-1972)	1233 (612-2140)	0.007
Weight z-score at birth, mean ± 1 SD	-1.02 ± 1.16	-1.29 ± 1.35	-1.23 ± 1.13	ns
SGA (n/N)	20/102	6/19	27/113	ns
Boys (n/N)	58/102	12/19	65/113	ns
Multiple birth (n/N)	27/102	11/19	51/113	ns

GA = gestational age, BW = birth weight, SGA = small for gestational age, ns = not significant

Table 2. Characteristics of group B NEC and stoma

Sex	**GA (week+days)**	**BW in gram**	**PMA at surgery**	**SBS**	**Number of days with PN**	**Nutrition at discharge**	**Age at stoma closure in weeks**	**Co-morbidity**
Girl	25+2	668	27+2	-	10	HM/TF	13	
Boy	24+5	764	27+0	-	10	PF	42	IVH4[1]
Girl	28+1	729	29+1	-	30	PF	15	Hydrocefalus
Boy	31+2	1972	31+4	-	12	HM	10	
Boy	24+5	709	27+3	-	14	HM/TF	29	
Girl	28+5	715	33+2	+	>365	PN/AAF/EF	14	
Girl	30+1	788	34+2	-	16	HM/TF	23	
Girl	28+4	1344	32+6	+	3	HM/AAF	23	
Boy	29+6	1350	33+3	-	15	HM/PF	23	
Girl	28+3	1140	34+5	-	5	-	17	
Girl	30+5	1060	30+6	+	183	PN/AAF/EF	26	
Boy	28+6	1160	33+6	-	12	HM	21	
Girl	27+4	1195	31+6	+	7	HM/HF/AAF	23	
Boy	27+4	930	27+6	-	7	HM	22	
Boy	27+6	1012	29+1	-	17	PF	23	
Boy	30+3	1679	32+0	-	9	HM/TF	14	
Boy	30+4	1271	30+5	-	4	HM	17	
Boy	25+5	888	26+1	-	13	HM	11	
Boy	26+5	700	29+1	+	-	-	23	BPD[2]

PMA = postmenstrual age (GA + weeks and days since birth), HM = human milk; PF = preterm formula (Enfalac®, Mead Johnson Nutritionals); TF = term formula; AAF = amino acid based formula (Neocate®, Nutricia); PN = parenteral nutrition; EF = energy dense formula (Infatrini®, Nutricia); HF = hypoallogenic term formula (Profylac®, Semper)

[1]IVH = intraventricular hemorrhage stage 4

[2]BPD = bronkopulmonal dysplasi

Table 3. Age at stoma formation / NEC surgery and stoma closure in group B

	GA at birth (weeks+days)	Age at surgery (weeks)	Age at surgery (PMA)	Age at stoma closure (weeks)	Age at stoma closure (PMA or CA)
Mean	28.2 (28+1)	2.5	30.7 (30+5)	20.6	48.8 (2m)
SD (weeks)	2.1	1.9	2.7	7.5	7.0
Median	28.4 (28+3)	2.3	30.9 (30+6)	21.6	50.1 (2.5m)
Min	24.7 (24+5)	0.1	26.1 (26+1)	10.6	36.9 (36+6)
Max	31.3 (31+2)	6.3	34.7 (34+5)	42.3	67.0 (6.7 m)

Median values are shown because the data is not normally distributed.

PMA = postmenstrual age (GA + weeks and days since birth) or CA = corrected age (weeks or months since birth. m = months. Term age is defined as 280 days = 40 weeks.