Outcome in neonates with necrotizing enterocolitis and patent ductus arteriosus

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Background: **There is no agreement of the influence of patent ductus arteriosus (PDA) on outcomes in patients with necrotizing enterocolitis (NEC). In this study, we assessed the influence of PDA on NEC outcomes.**

Methods: **A retrospective study of 131 infants with established NEC was performed. Outcomes (death, disease severity, need for surgery, hospitalization duration), as well as multiple clinical parameters were compared between NEC patients with no congenital heart disease (*n*=102) and those with isolated PDA (*n*=29). Univariate, multivariate and stepwise logistic regression analyses were performed.**

Results: **Birth weight and gestational age were significantly lower in patients with PDA [median (95% CI): 1120 g (1009-1562 g), 28.4 wk (27.8-30.5 wk)] than in those without PDA [median (95% CI): 1580 g (1593-1905 g), 32.4 wk (31.8-33.5 wk); *P*<0.05]. The risk of NEC-attributable fatality was higher in NEC patients with PDA (35%) than in NEC patients without PDA (14%)[univariate odds ratio (OR)=3.3, 95% CI: 1.8-8.6, *P*<0.05; multivariate OR=2.4, 95% CI: 0.82-2.39, *P*=0.111]. Significant independent predictors for non-survival within the entire cohort were advanced disease severity stage III (OR=27.9, 95% CI: 7.4-105, *P*<0.001) and birth weight below 1100 g (OR=5.7, 95% CI: 1.7-19.4, *P*<0.01).**

Conclusions: **In patients with NEC, the presence of PDA is associated with an increased risk of death. However, when important differences between the two study groups are controlled, only birth weight and disease severity may independently predict mortality.**

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Key words: **congenital heart disease; necrotizing enterocolitis; neonatal mortality; patent ductus arteriosus**

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Introduction

Since the first description of cardiogenic necrotizing enterocolitis in five patients with underlying congenital heart disease (CHD) by Polin et al in 1976,[1] there is increasing evidence that cardiogenic necrotizing enterocolitis is a distinct disease entity from NEC in the otherwise healthy preterm grower and feeder.[2,3] Within the group of neonates with heart failure, the patients who are premature with an isolated patent ductus arteriosus (PDA) are suggested to represent another subgroup of NEC, differing from those patients with other forms of CHD.[4]

The presence of NEC has an unclear effect on the mortality of patients with CHD.[5-7] Conflicting results are equally encountered in neonates with PDA. On one hand, NEC patients with PDA were found to have better outcomes as compared to NEC patients without PDA.[3] On the other hand, PDA was described to be associated with increased mortality in NEC patients.[8] However, the latter studies include suspected NEC,[3,8] potentially biasing outcome results due to the generally better outcome in patients with suspected NEC than patients with proven NEC. Thus, the question remains; in patients with NEC, does the presence of PDA increase the risk of a worse outcome?

The primary aim of the present study was to assess the risk for adverse outcome between NEC patients with or without PDA. We hypothesized that NEC outcomes vary according to the presence of PDA.

Methods

We retrospectively assessed data from an institutional database of infants with the diagnosis of acute NEC in a single tertiary perinatal center (Inselspital, University Hospital and University of Bern, Switzerland) over a 30 years period between January 1981 and October 2011 (n=196). Data analysis was preceded by local ethics committee approval. After exclusion of 65 patients with CHD other than PDA, spontaneous intestinal perforation, and suspected NEC (Bell stage I[9]) the datasets for 131 patients with confirmed NEC (Bell stage II or III) remained for final analysis. Bell staging was performed by review of patient charts including radiographies by three of five independent senior physicians (KU, CD, NM, KPM and BS).[9] Patients were admitted to the PDA group if clinical and echocardiographic findings concluded that there was a moderate or severe PDA.

Primary outcome variables were defined as death due to NEC, disease severity defined by Bell- stage,[9] need for surgery, and duration of hospital stay. Further analyzed variables were: gestational age [GA, weeks (wk)], birth weight [BW, grams (g)], percentile weight at birth (%), gender, twin birth, presence of perinatal asphyxia, need for postnatal intravenous sympathomimetic drugs, feeding habits [given as no enteral feeding from birth until the onset of NEC (NPO), formula feeding alone, or both formula and maternal milk (MM)], age at disease onset (d), routine laboratory parameters at disease onset (white blood cell count, immature to total neutrophil (IT)-ratio, hemoglobin concentration, platelet count, lactate concentration), treatment (surgical, medical), time from disease onset to surgery, need for a stoma, length of bowel affected, isolated small bowel affected, small bowel and colon affected, only colon affected, and histologic analysis from resections for acute disease. Hematoxylin and eosin-stained slides were assessed by two blinded independent senior physicians (SCS, KU) in a total of 32 patients. After omission of 7 cases due to the quality of the specimens, specimens of 21 patients without CHD and 4 patients with PDA were analyzed. Intestinal inflammation and coagulation necrosis were both graded from 0 to 4 according to a previously reported method.[10] Results are reported as principally inflammatory or principally coagulation-necrotic if difference in grading was ≥1 point for the respective pathological finding.

SPSS version 19 (IBM, SPSS, Chicago, IL, USA) was used for statistical analysis. Data were tested for normality and equal distribution via the Kolmogorov-Smirnov test and were assessed for skewness and kurtosis. Comparisons between groups were performed using analysis of variance (ANOVA) with Bonferroni- and Dunnett-T3-post-hoc analysis, student's t test or non-parametric test (as required, respectively) for continuous variables as well as the Chi-square test or Fisher's exact test (as required, respectively) for categorical variables.

To assess the influence of PDA, univariate and multivariate logistic regression analyses were performed for each outcome parameter. The continuous outcome variable and the length of hospital stay in survivors were transformed into a categorical variable using receiving operator characteristics (ROC) analysis for discrimination between patients without PDA and with PDA. ROC analysis resulted in an optimal cut-off of 65 days with a discriminative sensitivity of 70%, a specificity of 68%, and an area under the curve (AUC) of 0.61 [95% confidence interval (CI): 54%-81%]. Multivariate regression was adjusted for birth weight, gestational age, age at onset of NEC, and birth year. Independent predictors for non-survival were identified using a binary stepwise logistic regression model. Ideal birth weight cut-off was identified at 1100 g (AUC=0.76; 95% CI: 0.66-0.86). Data were expressed given as adjusted odds ratio (OR), or median and 95% CI of the mean for continuous variables, and frequencies for categorical variables unless otherwise specified. Two-sided tests were used throughout. P<0.05 was considered statistically significant.

Results

Of the 131 patients with confirmed NEC of Bell stage II or III, 102 had NEC without PDA and 29 had a moderate to severe PDA. BW and GA were significantly different between patient groups (Table 1). BW and

Table 1. Comparison of perinatal characteristics in NEC patients with or without PDA

Variables	No PDA (n=102)	PDA (n=29)	P value
Gestational age, wk	32.4 (31.8-33.5)	28.4 (27.8-30.5)	<0.001
Birth weight, g	1580 (1593-1905)	1120 (1009-1562)	0.001
Percentile weight, %	15 (25-38)	35 (23-52)	NS
Asphyxia, n (%)	5 (4.9)	0 (0)	NS
Twin, n (%)	16 (15.7)	4 (13.8)	NS
Female, n (%)	54 (53.5)	12 (41.4)	NS
Sympathomim., n (%)	13 (13.4)	8 (30.8)	NS
NPO, n (%)	1 (1.2)	2 (8.7)	NS
Formula alone, n (%)	16 (19.0)	4 (17.4)	NS
MM and formula, n (%)	36 (42.9)	49 (39.1)	NS

Data are n (% within the respective group) for categorical variables, and median (95% confidence interval) for continuous variables. sympathomim.: postnatal need for intravenous sympathomimetic drugs; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; NS: not significant. Feeding details are given as no enteral feeding from birth until the onset of NEC (NPO), formula feeding alone, or both formula and maternal milk (MM).

GA were lower in PDA patients [1120 g (1009-1562 g), 28.4 wk (27.8-30.5 wk)] than in patients without PDA [1580 g (1593-1905 g], 32.4 wk (31.8-33.5 wk)] (P<0.05). There was a non-significant trend for a higher rate of postnatal administration of sympathomimetic agents in PDA patients (30.8%) than in non-PDA patients (13.4%).

In patients without PDA age at diagnosis was lower (7 d, 8.4-12.8 d) than that in patients with PDA (14 d, 11.4-21.7 d, P<0.01, Table 2). Hemoglobin concentration at diagnosis was higher in patients without PDA (160 g/L, 153-167 g/L) than that in patients with PDA (146 g/L, 131-154 g/L, P<0.05).

There were no differences in surgical findings between patient groups (data not shown). Histologic grading resulted in equal proportions for inflammation (50%) versus necrosis (50%) in patients with PDA; in patients without PDA, there was a slight preponderance towards inflammation (62%) against coagulation necrosis (38%), however there was no significant difference between the two groups.

NEC-attributable mortality was significantly elevated in patients with PDA (34.5%) as compared to patients without PDA (13.7%, P<0.05). Univariate odds ratio for non-survival was significantly higher in the presence of a PDA (OR=3.3; 95% CI: 1.8-8.6; P=0.014, Table 3). This increased risk of mortality did not hold true when important differences between the two groups were controlled (multivariate OR=2.4; 95% CI: 0.82-2.39; P=0.111). Multivariate regression showed that birth year did influence neither the odds of death nor the length of hospital stay in PDA (Table 3). However, birth weight and gestational age assimilated the statistical significance of both the risk of death and the length of hospital stay in PDA patients (Table 3). Accordingly, a birth weight below 1100 g represented a significant independent predictor for non-survival as did advanced NEC stage (Table 4). Eight infants developed proven intestinal strictures, none of them having underlying PDA (not significant). Outcome parameters were not different between PDA patients receiving indometacin for PDA closure before onset of NEC (n=4) and those not receiving indometacin treatment before disease onset (n=25).

Table 2. Disease presentations and initial laboratory parameters in NEC patients with or without PDA

Variables	No PDA (n=102)	PDA (n=29)	P value
Age at disease onset, d	7.0 (8.4-12.8)	14.0 (11.4-21.7)	0.006
Bloody stools, n (%)	65 (69.1)	13 (56.5)	NS
Leukocyte count, g/L	9.9 (10.5-13.4)	12.2 (9.4-15.1)	NS
IT-ratio, %	10.0 (10.7-16.6)	15.8 (12.0-25.4)	NS
Platelet count, g/L	241 (233-290)	298 (224-337)	NS
Hemoglobin, g/L	160 (153-167)	146 (131-154)	NS
CRP, mg/dL	0 (5.3-16.6)	0 (1.0-12.9)	NS
Lactate level, n (%)	1.9 (1.9-3.2)	2.3 (1.4-5.4)	NS

Data are n (% within the respective group) for categorical variables, and median (95% confidence interval) for continuous variables. NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; hemoglobin: hemoglobin concentration; CRP: C-reactive protein; NS: not significant.

Discussion

In the present study, we found a trend towards worse outcome in NEC patients if they had PDA. The study is to our knowledge the first investigation on patients with NEC (Bell stage ≥II) without PDA (or other congenital heart faillure) and NEC patients with isolated PDA. There is only one study comparing outcome parameters between NEC in patients without PDA and those

Table 4. Independent predictors for non-survival in infants with necrotizing enterocolitis according to stepwise regression analysis

Variables	OR	95% CI	P value
Bell stage III	27.92	7.39-105	<0.001
Birth weight, ≤1100 g*	5.69	1.67-19.4	0.00
Birth year	1.08	1.02-1.15	0.013

OR: odds ratio; CI: confidence interval. *: The cutoff of 1100 g was chosen according to receiving operator characteristics curve analysis for comparison of birth weight between survivors and non-survivors.

Table 3. Univariate and multivariate risk of adverse outcome in NEC patients with or without PDA

Outcome	No PDA n=102	PDA n=29	Univariate OR (95% CI), P value	Multivariate OR (95% CI), P value*	Multivariate OR (95% CI), P value†
Death due to NEC, n (%)	14 (13.7)	10 (34.5)	3.31 (1.82-8.56), 0.014	3.31 (1.24-8.79), 0.017	2.39 (0.82-2.39), 0.111
Bell stage III, n (%)	18 (17.6)	7 (24.1)	1.49 (0.55- 4.00), 0.434	1.49 (0.55-4.01), 0.435	0.67 (0.25-2.82), 0.430
Need for surgery, n (%)	46 (45.1)	16 (55.2)	1.26 (0.55-2.88), 0.586	1.22 (0.51-2.91), 0.657	0.67 (0.29-1.53), 0.340
Hospitalization 65 d in survivors,‡ n (%)	34 (44.1)	22 (75.9)	3.98 (1.56-10.20), 0.004	4.65 (1.68-12.84), 0.003	2.1 (0.68-6.46), 0.198

Data are n (% within the respective group) for categorical variables, and median (95% confidence interval) for continuous variables. OR: odds ratio; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; CI: confidence interval. *: Adjustment of the multivariate model includes birth year; †: Adjustment of the multivariate model includes gestational age and birth weight; ‡: The cutoff of 65 days was chosen according to receiving operator characteristics curve analysis for comparison of duration of hospitalization between patients with or without PDA.

with PDA, reporting better outcomes in infants with PDA.[3] In contrast to the work of Pickard et al[3] we omitted a major inclusion bias in the present study by only including confirmed NEC cases. Pickard et al[3] potentially flawed their results because 36% of their patients with PDA had NEC stage I but only 19% in the non-PDA group had NEC stage I. The higher rate of "unconfirmed" or "suspected" NEC cases in their PDA group might be an explanation for the better outcome of patients in the PDA group, indicating that outcome in suspected NEC stage I would be better than in confirmed NEC stage II or III. We conclude that the presence of PDA does not improve outcome in patients with confirmed NEC, with a mortality risk that increases from 14% in patients without PDA to 35% in patients with PDA. However, higher mortality risk in PDA patients was only significant in univariate analysis. When important differences between the two study groups were controlled by multivariate analysis, this effect was not statistically significant.

Hence, we found some further significant differences between non-PDA and PDA NEC patients supporting the hypothesis of different disease entities. First, gestational age and birth weight were lower in patients with PDA. This observation is in accordance with the results from Pickard and coworkers.[3] Second, age at disease onset was higher in the PDA group (median 14 d) than that in the non-PDA group (median 7 d, $P<0.05$). This finding is in accordance with the data reported by Gonzalez-Rivera and colleagues, who described an inverse correlationship between timing of disease onset and gestational age.[11] Pickard et al[3] described equivalent medians for disease onset in NEC patients without (10 d) or with PDA (14 d) as compared with our data. Third, we found a non-significant trend towards more histologic intestinal inflammation in the non-PDA NEC patients, supporting different pathophysiological entities. To our knowledge, we did not find another report comparing intestinal inflammation and coagulative necrosis in NEC patients with or without PDA. Nevertheless, it is well-known that abdominal aortic flow reversal is associated with an increased risk of NEC.[12] Unfortunately the trend towards intestinal inflammation in non-PDA NEC could neither be confirmed neither by different levels of laboratory parameters at disease onset nor by macroscopic intraoperative findings.

An argument against an etiopathologic contribution of PDA to intestinal ischemia and disease outcome is that in our study PDA was not an independent predictor for non-survival in stepwise multivariate regression analysis in contrast to disease severity and birth weight. The present study has several limitations. The retrospective study design engenders several potential sources for bias. In addition the long inclusion period over 30 years bears a multitude of possible confounders flawing results e.g. changing intensive care protocols, other feeding habits, and different surgical approaches. We found that the duration of inclusion did not have a major influence on the assessed outcome parameters because inclusion of birth year in multivariate analysis did not change the risk for mortality. Additionally, other investigators have found that mortality was stable in a study of 360 NEC patients between 1986 and 1999, which supports our findings.[13] Also we present a small number of PDA patients resulting in low statistical power. And the results on mortality were not statistically significant in multivariate analysis. The finding that the presence of PDA does not worsen outcome in patients with NEC is in line with the results of the only study with a similar number of patients with confirmed NEC by Pickard et al.[3] Finally, we do not have data on flow parameters, the ultimate proof of intestinal circulatory disturbance. However it was not the primary aim of the study to elucidate disease etiologies in NEC patients with PDA.

In conclusion, in patients with established necrotizing enterocolitis, the presence of PDA is associated with an increased risk for longer hospital stay and death. Disease severity and birth weight may independently predict mortality.

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Contributors: KU conceptualized (together with BS), designed and coordinated the study, reviewed patient charts, participated in histologic analyses (together with SCS), carried out the statistical analyses, wrote the first draft as well as the subsequent drafts of the manuscript, and approved the final manuscript as submitted. SF carried out data collection, participated in statistical analyses, critically revised the manuscript, and approved the final manuscript as submitted. CD coordinated and supervised data collection (together with KPM), reviewed patient charts, critically revised the manuscript, and approved the final manuscript as submitted. NM supervised data collection, reviewed patient charts, critically revised the manuscript, and approved the final manuscript as submitted. SSC carried out the histologic analyses (together with KU). He critically revised the manuscript, and approved the final manuscript as submitted. KPM coordinated and supervised data collection (together with CD), reviewed patient charts, critically revised the manuscript, and approved the final manuscript as submitted. BS conceptualized the study (together with KU), reviewed patient charts, critically revised the manuscript, and approved the final manuscript as submitted.

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