Patent ductus arteriosus treatment in very preterm infants: a European population-based cohort study (EPICE) on variation and outcomes

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ABSTRACT

Background: Spontaneous closure of patent ductus arteriosus (PDA) occurs frequently in very preterm infants and despite the lack of evidence for treatment benefits, treatment for PDA is common in neonatal medicine.

Objectives: To study regional variation in PDA treatment in very preterm infants (≤31 weeks gestational weeks), its relation to differences in perinatal characteristics and associations with bronchopulmonary dysplasia (BPD) and survival without major neonatal morbidity.

Methods: Population-based cohort study in 19 regions in 11 European countries 2011-2012. 6,896 infants with data on PDA treatment were included. Differences in infant characteristics were studied across regions using a propensity score derived from perinatal risk factors for PDA treatment. Primary outcomes were a composite of BPD or death before 36 weeks postmenstrual age, or survival without major neonatal morbidity.

Results: The proportion of PDA treatment varied from 10 to 39% between regions ($p<0.001$). and this difference could not be explained by differences in perinatal characteristics . Regions were categorized according to low (<15%, n=6), medium (15-25%, n=9) or high (>25%, n=4) proportion of PDA treatment. Infants treated for PDA, compared to not treated, were at higher risk of BPD or death in all regions, with an overall propensity score adjusted risk ratio of 1.33 (95% confidence interval 1.18-1.51). Survival without major neonatal morbidity was not related to PDA treatment.

Conclusions: PDA treatment varies largely across Europe without associated variations in perinatal characteristics or neonatal outcomes. This finding calls for more uniform guidance for PDA diagnosis and treatment in very preterm infants.

ABBREVIATIONS

aRR	adjusted risk ratio
CI	confidence interval
BPD	bronchopulmonary dysplasia
cPVL	cystic periventricular leukomalacia
EPICE	Effective Perinatal Intensive Care in Europe
GA	gestational age
IQR	interquartile range
IVH	intraventricular hemorrhage
NEC	necrotizing enterocolitis
NSAID	non-steroidal anti-inflammatory drug
RR	risk ratio
RDS	respiratory distress syndrome
PDA	patent ductus arteriosus
PMA	postmenstrual age
pPROM	preterm premature rupture of membranes
SGA	small for gestational age
ROP	retinopathy of prematurity

INTRODUCTION

Patent ductus arteriosus (PDA) is common in very preterm infants (≤31 gestational weeks, GW) and is associated with systemic hypoperfusion that may increase the risk of intraventricular haemorrhage (IVH) and necrotizing enterocolitis (NEC).[1, 2] A hemodynamically significant PDA may cause pulmonary congestion and increase the risk of bronchopulmonary dysplasia (BPD).[3] Many clinicians therefore attempt pharmacological or surgical PDA closure in infants with a hemodynamically significant PDA.

In spite of extensive research including clinical trials, it has been difficult to provide evidence for improved outcomes after PDA treatment, partly because of the high spontaneous closure rate and the high incidence of open label treatment.[4, 5, 6, 7, 8] Other remaining questions regarding PDA treatment include optimal timing of treatment [9, 10] and subsequent long-term outcome.[11, 12]

Conditions with large variations in management may benefit from increased standardization to improve care.[13] We hypothesized that PDA management belongs to this category and that there are significant differences in PDA treatment in very preterm infants between different European regions. To test our hypothesis, we studied variations in PDA treatment in a large European population-based cohort. Secondly, we investigated how differences in PDA treatment are associated with differences in perinatal characteristics between the regions. Finally, we assessed the association between PDA treatment and risk of BPD or death, or survival without major neonatal morbidity.

METHODS

The EPICE (Effective Perinatal Intensive Care in Europe) Cohort Study is a population-based study of all births between 22+0 and 31+6 weeks gestation in 19 regions across 11 European countries in 2011-2012 (www.epiceproject.eu). Inclusions occurred over 12 months except in France (6 months). Infants who survived ≥ 24 hours after birth were included in this study. Fifteen of the 247 neonatal units with >20% missing data on PDA treatment were excluded (431 infants from 5 regions in 4 countries). The final study sample included 6,896 infants, Figure 1. There were no significant differences in gestational age, birth weight, infant sex or mortality between infants included and those excluded (N=509).

Exposures

PDA treatment was defined as any non-steroidal anti-inflammatory (NSAID) treatment (ibuprofen or indomethacin) or surgery to close the PDA. Surgical treatment was categorized as either primary surgery or surgery following prior medical treatment. Postnatal age in days at the start of treatment was recorded.

Diagnosis of PDA was based on clinical and/or echocardiographic assessment. We did not collect information on how PDA was diagnosed in the individual infant. Of the included units, 95.1 %, caring for 6768 (98.1%) of the included infants, could perform echocardiography on-site.

Outcomes

Infant outcomes were: a) a composite outcome of BPD (any oxygen treatment at 36 weeks postmenstrual age (PMA)) or death before 36 weeks gestation, and b) survival without major neonatal morbidity (IVH grade ≥3, cystic periventricular leukomalacia (cPVL), NEC requiring surgery or peritoneal drainage, or retinopathy of prematurity (ROP) stage ≥3). Data were

collected on each infant until death or hospital discharge (median PMA at discharge: 37.4 weeks (interquartile range, IQR 36.0-39.1).

Covariates

Covariates selected for the analyses were: maternal age; multiple pregnancy; preeclampsia/eclampsia; spontaneous onset of labour; preterm premature rupture of membranes (pPROM); maternal infection as indication for delivery, administration of any antenatal corticosteroids; cesarean section; infant sex; GA at birth, small for GA (SGA; categorized as birth weight<3rd or between 3rd to <10th percentiles for GA and sex using Hadlock's references adapted to regional population values using Gardosi's model)[14, 15], use of mechanical ventilation (started on first day of life or total duration among survivors to ≥36 weeks PMA); and number of septicemias confirmed by blood culture.

Ethical approval and informed parental consent (active or passive, depending on each participating country's national legislation) for data collection were obtained in each study region. EPICE regions were selected in part because of the existence of preexisting data collection systems for routine monitoring of births which made it possible to collect data on all very preterm births. In the French regions, EPICE was carried out as part of the EPIPAGE 2 study and parents had to consent to all parts of data collection, leading to 6.4% of total births for whom consent could not be obtained, including also stillbirths and terminations of pregnancy. The European study was also approved by the French Advisory Committee on Use of Health Data in Medical Research (CCTIRS) and the French National Commission for Data Protection and Liberties (CNIL).

Statistical analyses

Descriptive data are displayed as median (interquartile range;IQR) for continuous data and percentage (n, %) for categorical data. Differences between groups were tested using Kruskal-Wallis test for continuous data, and Chi squared test for proportions. Associations between covariates and risk of PDA treatment were analysed in mixed-effects generalized linear regression models adjusted for gestational age and with neonatal unit as the random effect variable and reported as risk ratios (RR) with 95% confidence intervals (CI).

Differences in perinatal characteristics between the regions were explored by calculating a propensity score for PDA treatment, i.e., a single index variable summarizing the maternal and perinatal characteristics for each subject known or hypothesized to be either related to the exposure (PDA treatment) or the outcomes. The propensity score was calculated by fitting a logit model using the *pscore* command in STATA 13.1 including the covariates in online supplementary Table 1. The adequacy of the model was checked by evaluating the balance of the covariates across treatment groups.

Clustering of data was handled by using a mixed-effects generalized linear regression model to analyze the association between PDA treatment and the composite outcome of BPD or death; and PDA treatment and survival without major neonatal morbidity as defined above. In supplementary analyses, clustering on mothers (for multiples) was evaluated by adding maternal identity as a second random effect level in the mixed-effects regression. Results from these regression analyses are reported as propensity score adjusted risk ratios (aRR) with 95% CI. In supplementary analyses of the association between PDA treatment and BPD in survivors, the results were further adjusted for total duration of mechanical ventilation and number of confirmed septicemias. All data were analyzed in STATA 13.1(www.stata.com).

RESULTS

The study sample consisted of 6,896 infants (54% male) with a mean (SD) GA of 29.1 (2.2) weeks and a mean birth weight of 1,223 (384) grams. Of these, 1,968 (28.5%) were born at <28 weeks and 4,928 (71.5%) between 28 and 31 weeks gestation. The total incidence of any PDA treatment was 20% for the whole cohort; 44% for infants <28 weeks and 9.8% for infants born at 28-31 weeks gestation.

Pregnancy and neonatal factors associated with PDA treatment

Cohort characteristics by type of PDA treatment are presented in Table 1. GA was strongly associated with PDA treatment. At 23 weeks gestation, 60% of the infants received PDA treatment compared with 3.5% at 31 weeks, p<0.001 (online supplementary Figure 1). After adjustment for GA, cohort characteristics associated with a higher risk for PDA treatment were multiple pregnancy, preeclampsia/eclampsia, cesarean delivery, SGA, and neonatal septicemia. Cohort characteristics associated with a lower risk were pPROM, spontaneous onset of delivery, and infection as indication for delivery. Maternal age and use of antenatal corticosteroids were not associated with PDA treatment (online supplementary Table 2).

Regional variations in PDA treatment

Between regions, the overall proportion of PDA treatment varied from 10 to 39% (p<0.001), Figure 2. In infants born before 28 weeks gestation, the proportion of PDA treatment varied from 27 to 82% (p<0.001). The corresponding variation among infants born at 28-31 weeks was 2.9 to 26% (p<0.001). Regional variations in type of PDA treatment are shown in online supplementary Figure 2.

Based on the distribution of PDA treatment proportions, regions were categorized as low (<15%; (n=6), medium (15-25%; n=9) or high proportion (>25; n=4) (Figure 2). Regions with a

high proportion of treated infants started pharmacological treatment earlier, and used PDA surgery more often than regions with low or medium proportions of PDA treatment. In addition, high proportion regions used primary PDA surgery at a lower postnatal age than low and medium treatment regions. Regions with high proportion of PDA treatment had the highest access to PDA surgery on site without transfer, but also medium proportion regions had higher access to PDA surgery on site than regions with low proportion of treatment, Table 2. There were no differences in postnatal age at start of pharmacological between infants born before 28, or at 28-31 weeks gestation (data not shown).

PDA treatment and perinatal characteristics

Differences in perinatal characteristics, measured as propensity scores for PDA treatment, did not explain the variations in treatment observed between the regions. Regions with a low proportion of treatment had slightly higher propensity scores (median 0.45; IQR 0.34 - 0.56) for treatment among infants <28 weeks gestation compared with regions with medium (median 0.42; IQR 0.31-0.55, p= <0.001) or high PDA treatment (median 0.42; IQR 0.35-0.48, p = 0.02). Among infants born at 28-31 weeks, regions with low and medium PDA treatment proportions had similar scores (median propensity score 0.07 (IQR 0.04-0.13), p=0.45). Regions with high proportion of PDA treatment had higher propensity scores than both low and medium regions, (median 0.09; IQR: 0.05-0.17, p<0.001 for both comparisons), Figure 3.

PDA treatment and neonatal outcome

Infants treated for PDA were at higher risk of BPD or death with an overall propensity score adjusted RR (aRR) of 1.33 (95% confidence interval 1.18-1.51). PDA treatment was associated with an increased aRR of BPD or death in all regions. The highest risks were observed among infants undergoing primary surgery; with an adjusted risk increase of 45% in regions with low

proportions of PDA treatment, 79% in regions with medium proportions, and 176% in regions with high proportions of PDA treatment. These risks were accentuated when restricting the analyses to study BPD among survivors to 36 weeks PMA. Further adjustment for duration of mechanical ventilation and number of confirmed septicemias slightly attenuated the association between PDA treatment and BPD, but a risk increase for BPD of 34, 67 and 154% remained, in low, medium and high treatment regions respectively (online Table 3). There was no association between PDA treatment and survival without major neonatal morbidity, regardless of region, Table 3. Adjustment for clustering on mothers in multiples did not change the estimates.

DISCUSSION

In this population-based study of very preterm infants across Europe, we found that PDA treatment varied three- (<28 weeks) to ninefold (28-31 weeks) between different regions. This regional variation was not explained by differences in perinatal characteristics. Our data confirm previous observations [16, 17] that GA is the most important predictor for PDA treatment, with a sharp decrease in PDA treatment from 23 to 31 weeks gestation. The risk of BPD or death in infants treated for PDA was increased compared with untreated infants, and the association between PDA treatment and BPD further strengthened when restricting analyses to survivors to ≥36 weeks gestation. Finally, PDA treatment was not associated with survival without major neonatal morbidity.

The incidence of any PDA treatment in EPICE was similar to that in other population-based European studies [18], [16, 19], and slightly lower than reported in Canada and Japan.[20] In the NICHD Neonatal Research Network in the US, the proportion of infants <28 weeks with a PDA diagnosis varied from 26-78% between different centers in 2003-2007, with a threefold

variation in use of pharmacological treatment and a fourfold difference in PDA surgery, but data permitting more detailed understanding of variations were lacking.[17] In EPICE, we found that differences in perinatal characteristics between the regions did not explain the variations in PDA treatment.

The evidence-base for PDA treatment is weak and has been debated in the last decade [5, 21, 22]. The large regional variation in treatment in EPICE could be driven by different treatment guidelines (or their absence) and use of echocardiography may differ between centers. Furthermore, the definition of a hemodynamically significant PDA may vary.[23] Recent data show that early PDA screening is associated with higher rates of PDA treatment, but lower in-hospital mortality.[24] Nevertheless, the lack of an association between PDA treatment and improved neonatal outcome supports the questioning of liberal PDA treatment. It should also be noted that up to 26% of infants born at 28-31 weeks were treated for PDA in some regions, which cannot be considered evidence-based given the high spontaneous closure rate [7].

Whereas PDA treatment was found to be associated with an increased risk of BPD or death, this study cannot provide evidence for an underlying explanation. The severity of respiratory distress syndrome (RDS) may have determined both the risk of PDA treatment and of BPD. In addition, both PDA and BPD are linked to conditions of inflammation - before and after birth - such as pPROM and neonatal infections[25].

The highest risk for BPD or death was seen after PDA surgery. This association may have suffered from confounding by indication. However, given earlier findings of a strong association between PDA surgery and BPD risk [3] and the large increases for BPD or death associated with surgery in our study, we cannot exclude that the surgical procedure per se or other factors may contribute to this increased risk.

The age at PDA surgery following prior medical PDA treatment did not differ between low, medium or high treatment regions. However, primary surgery was performed 2-3 weeks earlier in high compared to low and medium treatment regions. In high treatment regions, access to PDA surgery onsite was also higher. This could indicate that centers in high treatment regions have adopted a more proactive, early surgical approach, while the other regions use primary surgery more restrictively.

High treatment regions used earlier pharmacological PDA treatment than the other regions. Timing of pharmacological PDA treatment after extremely preterm birth has in other studies not been associated with the risk of PDA surgery or death, and expectant PDA management has not been associated with increased risk of BPD[26], although contradictive observations have been reported[27]. We hypothesize that early timing of treatment may be one of the underlying factors leading to higher treatment incidence, since spontaneous closure may not occur until after an early treatment decision has been made. This hypothesis is supported by the fact that the infants born at 28-31 weeks gestation were treated at the same postnatal age as infants born at <28 weeks gestation.

Strengths of this cohort study include the population-based design, the standardized data collection and the large number of infants, regions and countries included. Detailed data on PDA treatment were available and we believe that our results are generalizable to most European neonatal intensive care settings.

The main limitation is the lack of echocardiographic PDA characteristics, which hinders us from knowing the PDA incidence in the untreated group, and to study the hemodynamic significance of the PDA in infants receiving treatment. Although there may be differences in the incidence of hemodynamically significant PDA between the regions, we do not think that such potential

differences could be the only explanation for a fourfold difference in PDA treatment between the regions.

Further, it is a limitation that we could not take neonatal disease burden into account in our propensity score model for PDA treatment. To avoid confounding, it is essential that factors used to predict treatment occur before the treatment. Since we did not have the exact dates of diseases, such as sepsis, or start and stop date of each episode of mechanical ventilation we could not use these factors in the propensity score. Although we could not disentangle the temporal relationships with PDA treatment, adjusting for total duration of mechanical ventilation and number of confirmed septicemias in supplementary analyses did not change the association between PDA treatment and an increased risk of BPD. Possible residual confounding and confounding by indication are additional limitations. Finally, we did not register if paracetamol had been administered to the infants.

In conclusion, there is a fourfold variation in PDA treatment rates between European regions that could not be explained by differences in perinatal characteristics between regions. Liberal treatment was not associated with a lower risk of BPD or death, nor was it associated with a higher chance of survival free of major neonatal morbidity. It is also notable that an important proportion infants born at 28-31 weeks is treated for PDA although the spontaneous closure rate is known to be high in this group. These findings support a call for uniform guidance for the management of PDA in very preterm infants.

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AUTHOR CONTRIBUTIONS

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Study concept and design, and acquisition, analysis, or interpretation of data: All authors and the EPICE research group.

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CONFLICTS OF INTEREST

None of the authors have any conflicts of interest to declare.

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FIGURE LEGENDS

Figure 1. Flow chart of inclusions and exclusions and PDA treatment in the EPICE cohort. Final study sample included 6896 infants born at ≤31 weeks gestation in Europe.

Figure 2. Categorization of regions into low (<15%), medium (15-25%) and high (>25%) proportion of PDA treatment in the EPICE cohort. N=6896 infants born at ≤31 weeks of gestation.

Figure 3. Distribution of propensity scores for PDA-treatment by group of regions (low, medium and high proportion of PDA-treatment), and actual proportion of PDA-treatment in infants born at <28 weeks and from 28 to 31 weeks gestation. The boxes indicate the 25^{th} to 75 th percentiles, the whiskers the 10^{th} and 90^{th} percentiles. Values below or above the 10^{th} and 90^{th} percentiles are indicated with dots.