Early Human Development 190 (2024) 105953

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Role of patent ductus arteriosus in preterms in long-term outcome

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ARTICLE INFO

Keywords:
Patent ductus arteriosus
Neurodevelopmental outcome
Cerebral oxygenation

ABSTRACT

Objective: This study aimed to determine long-term neurodevelopmental outcome and cerebral oxygenation in extremely preterm infants, comparing those with a hemodynamic significant patent ductus arteriosus (hsPDA) to those without.
Study design: We included infants born before 28 weeks of gestation from 2008 to 2010 with routine echocardiography. Prior to echocardiography, regional cerebral oxygen saturation was measured. At 5 years of age, we evaluated neurodevelopmental outcomes using the Movement Assessment Battery for Children 2nd Dutch edition for motor skills and the Wechsler Preschool and Primary Scale of Intelligence 3rd Dutch edition for cognition.
Results: A total of 66 infants (gestational age 26.6 ± 0.9 weeks, birth weight 912 ± 176 g) were included, 34 infants with a hsPDA (including treatment). The group infants with hsPDA showed lower pre-closure cerebral saturation levels (58.2 % ±7.8 % versus 62.8 % ±7.0 %; $p = 0.01$). At 5 years, impaired motor outcome occurred more often in infants with hsPDA (17 (53 %) vs. 7 (23 %); $p = 0.01$). In multivariate analysis existence of hsPDA remained unfavourably related to the motor subdomain "aiming and catching". There were no potential effects of hsPDA on cognitive performance at 5 years of age.
Conclusion: Treatment-receiving infants with hsPDA appear to exhibit motor deficits, specifically in "aiming and catching", by the age 5. Persistent ductal patency could be a contributing factor.

1. Introduction

A hemodynamically significant patent ductus arteriosus (hsPDA) affects almost half of the neonates born <28 weeks of gestational age (GA) [1]. At present, an expectant management approach towards ductal closure is increasingly common practice, which "translates" itself into a delay of (surgical) closure of the duct [2–4]. There is, however, limited data regarding the impact of the prolonged patency of hsPDA on brain development and neurodevelopmental outcome [5]. Earlier studies reported smaller cerebellar volumes and a suboptimal neurodevelopmental outcome at 2 years of age in extremely preterm infants whose ducts were eventually surgically closed [6–8]. A recent study of our group theorized that the duration of hsPDA rather than the surgical procedure itself was independently related to suboptimal brain growth and neurodevelopmental outcome, although low cerebral oxygen saturation (< 45 %) could not be excluded here as a possible concomitant factor [9]. These studies were, however, performed in a selected population of extremely preterm infants whose duct was exclusively closed surgically and not in an unselected population of preterm infants with hsPDA.

In this study, we aimed to assess neurodevelopmental outcome and cerebral oxygenation in an unselected cohort of extremely preterm infants with and without hsPDA. Since more subtle deficits in cognitive and motor functioning become apparent at early school age, we determined neurodevelopmental outcome at 5 years of age [10,11].

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https://doi.org/10.1016/j.earlhumdev.2024.105953
Received 8 November 2023; Received in revised form 28 January 2024; Accepted 29 January 2024
Available online 1 February 2024
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Abbreviations

GA	gestational age
hsPDA	hemodynamically significant patent ductus arteriosus
M-ABC(2)-NL	Dutch Movement Assessment Battery for Children, Second Edition
NEC	necrotizing enterocolitis
PIVH	peri-intraventricular hemorrhage
PLDcort	preterm lung disease with the necessity of additional treatment with postnatal corticosteroids
PNA	postnatal age
$rScO_2$	regional cerebral oxygen saturation
WPPSI-III-NL	Dutch Wechsler Preschool and Primary Scale of Intelligence, Third Edition

2. Methods

2.1. Patients

From a cohort of 380 preterm infants of <32 weeks GA, in which the association between cerebral oxygenation and echocardiographic parameters was analysed [12], all infants with GA <28 weeks were selected ($n = 78$. Infants with hemodynamically significant congenital heart defects or chromosomal abnormalities were excluded.

Patient characteristics were collected from hospital records. Preterm lung disease (PLDcort) was defined as the necessity of additional treatment with postnatal corticosteroids, since these infants conventionally depend on prolonged mechanical ventilation and are prone to develop bronchopulmonary dysplasia. Additionally, neonatal corticosteroid use might be associated with suboptimal brain development and neurodevelopmental outcome [13]. Corticosteroid treatment consisted of hydrocortisone for a total duration of 22 days. An initial dosage of 5 mg/kg/day in four doses per day was started for 7 days, followed by 3.75 mg/kg/day in three doses per day for 5 days. Thereafter, the frequency was lowered by one dosage every five days [14].

Periventricular/intraventricular hemorrhage (PIVH) was graded according to the classification of Papile and was defined as severe if grade 3 or 4. Neuropsychological assessment at 5 years of age is standard care in our follow-up program for all preterm infants with GA <28 weeks. The institutional review board of the University Medical Center Utrecht ruled that this study was exempt from the Medical Research Involving Human Subjects Act. Parental consent for using patient data was obtained.

2.2. Diagnosis of hsPDA

As part of the original cohort study, three routine echocardiographic examinations were performed on the second, fourth and sixth day after birth [12]. Results were blinded for the attending neonatologist. The ultrasound results were unblinded when clinical suspicion of hsPDA arose, with symptoms such as (increased) need for respiratory support, cardiac murmur, or feeding intolerance. A hsPDA diagnosis was based on minimal ductal diameter > 1.4 mm/kg, and at least 2 of the following parameters: a) growing or pulsatile ductal flow pattern; b) left pulmonary artery-end diastolic flow>0.2 m/s; c) left atrial to aortic root ratio > 1.4 mm [15]. When there was spontaneous ductal closure during the first week or when the patent duct was not fulfilling criteria during this period, this was classified as NohsPDA.

hsPDA treatment decisions were made by the attending neonatologist based on our intensive care guidelines. At time of the study, the initial treatment was indomethacin (3 intravenous doses of 0.2 mg/kg every 12 h). A maximum of three courses were administered when the duct appeared responsive but was not yet fully closed. Surgical ligation was performed when indomethacin was contraindicated (see Supplemental Table 1) or when pharmacological intervention failed. In addition, postnatal age (PNA) in days at time of hsPDA diagnosis and until hsPDA closure was recorded.

2.3. Long-term neurodevelopmental outcome

Neurodevelopmental outcome was evaluated at 5 years of age, as part of standard care. Motor performance was assessed with the Movement Assessment Battery for Children, Second Dutch Edition (M-ABC (2)-NL) by a pediatric physiotherapist [16]. The M-ABC(2)-NL consists of eight scoring items evaluating three different domains: manual dexterity (3 items), aiming and catching (2 items), and balance (3 items), of which a total test score is calculated. Based on percentile scores (PS) of the total test score, three different categories can be distinguished: normal motor function (PS > 16), borderline motor impairment (6 ≤ PS ≤ 16), and significant motor impairment (PS < 6). The last category was defined as poor motor outcome in our study. The M-ABC(2)-NL scores were interpreted according to specified norms for the Dutch population.

Cognition was evaluated by a pediatric psychologist with the Dutch version of the Wechsler Preschool and Primary Scale of Intelligence, Third Dutch Edition (WPPSI-III-NL) [17]. The WPPSI-III-NL measures 3 items: verbal intelligence quotient (IQ), performance intelligence quotient (IQ), and processing speed quotient (mean 100; SD ± 15). The verbal and performance IQ are combined to determine a full-scale IQ. Cognitive outcome was defined as less favourable when the full-scale IQ-score was below −1 SD (<85).

2.4. Cerebral oxygen saturation

Regional cerebral oxygen saturation ($rScO_2$) in % was monitored by the INVOS 5100C near-infrared spectroscopy monitor (Medtronics, Minneapolis, MN) with the small adult sensor (SomaSensor SAFB-SM, Covidien, Mansfield, MA) on the fronto-parietal side of the infants' head prior to each echocardiographic examination, per study protocol [12]. Monitoring $rScO_2$ is standard practice in our intensive care for all preterm infants born <30 weeks GA for at least 72 h after birth. Hereafter, the $rScO_2$-sensor was re-applied before each cardiac ultrasound. A period of 1 h reliable $rScO_2$ monitoring was selected before the cardiac ultrasound on which hsPDA was diagnosed. In the group infants without hsPDA, a similar 1 h period was selected prior to the second ultrasound as a comparison.

2.5. Statistical analysis

Data are presented as mean (±SD), median (range or IQR), or count (%), where appropriate. Clinical characteristics, cerebral oxygenation, and neurodevelopmental outcome were compared between the group of infants with hsPDA (hsPDA) and without hsPDA (NohsPDA) with the Chi-square test and independent samples *t*-test (or the Mann-Whitney *U* test). Poor motor and cognitive outcome were compared with independent samples t-test or the Mann-Whitney U test.

Multivariate linear regression (MLR) analysis was performed to investigate the association between the different neurodevelopmental outcome scores, the diagnosis of hsPDA (hsPDA yes/no), and possible relevant variables regarding their impact on neurodevelopmental outcome: GA, severe PIVH (≥ grade 3), PLDcort, and $rScO_2$. MLR-models were constructed with motor outcome (Model 1) and cognitive outcome (Model 2) as the dependent variables, and GA, severe IVH (yes/no), PLDcort (yes/no), $rScO_2$ (%), and hsPDA (yes/no) as the independent variables. Additional models were constructed with the different subdomains of motor outcome (Model 1A-C) and cognitive outcome (Model 2A-C) as dependent variables.

To eliminate the potential effect of ductal surgery another MLR subanalysis was performed. Comparable MLR-models were constructed in which ten hsPDA patients, who received surgical closure of the duct,

were excluded (Model 3A-C and Model 4A-C).

All data were checked for collinearity. Results of MLR analysis are presented as coefficients and *p* values of the independent variables.

A post hoc analysis was performed on the subgroup of preterm infants with hsPDA to evaluate the effect of specific ductal characteristics. Surgical treatment (yes/no), duration of hsPDA (postnatal age at time of ductal closure) and $rScO_2$ values (before ductal closure) were selected as potential variables influencing neurodevelopmental outcome. MLR analysis was performed between these independent variables with motor (Model 5A-C) and cognitive outcome (Model 6 A-C) scores as dependent variables.

For all analyses a *p* value of <0.05 was considered statistically significant.

3. Results

Of the 78 extremely preterm infants, seven infants died (all before one month of age: four infants due to severe respiratory complications, one infant from a perforated necrotizing enterocolitis (NEC) and two infants had severe neurological complications). Five infants were lost to follow-up (of which 2 move out of our care region) for any outcome assessment at 5 years of age, resulting in a total of 66 included patients. Of these 66 infants, 63 infants received an assessment with the M-ABC (2)-NL and 56 infants with the WPPSI-III-NL (see Fig. 1).

The clinical characteristics of the included infants are shown in Table 1. After the first week of life the duct closed spontaneously in twenty-four infants. Ductal patency remained in eight infants which was considered not hemodynamically significant. The other thirty-four infants developed a hsPDA, which were all deblinded (because of symptoms) and received treatment afterwards. Four infants were primarily surgically ligated due to contraindications for indomethacin. Six infants received surgical ligation after failure of medical treatment. Median PNA at ductal diagnosis was 3.0 days [range 1–10 days] and at ductal closure 8.0 days [range 2–14 days]. Median PNA at primary ductal surgery was 7.0 days [range 2–10 days]. Two infants developed a vocal cord paresis after ductal surgery.

Infants who developed hsPDA had a lower GA and were sicker, with significantly higher rates of severe PIVH. $rScO_2$ was lower in infants with a hsPDA (mean ± SD; 58.2 % ±7.8 % versus 62.8 % ±7.0 %; $p = 0.01$).

Table 1
Clinical characteristics of the included patients.

	NohsPDA *n* = 32	hsPDA *n* = 34	*p* value
Male gender, n (%)	18 (56)	23 (68)	0.34
Gestational age (weeks), mean ± SD	26.9 ± 0.8	26.4 ± 1.0	0.03
Birth weight (g), mean ± SD	955 ± 139	900 ± 203	0.10
Apgar 5 min, median [range]	8 [5–10]	8 [3–9]	0.32
Completed course of antenatal corticosteroids, n (%)	29 (91)	28 (82)	0.48
PLDcort, n (%)	5 (16)	9 (27)	0.28
Sepsis early- and late-onset, n (%)	10 (31)	14 (41)	0.40
Severe PIVH, n (%)	1 (3)	6 (18)	0.05
Inotropic support, n (%)	15 (47)	20 (59)	0.33
$rScO_2$ (%), mean ± SD	62.8 ± 7.0	58.2 ± 7.8	0.01
PNA at diagnosis (days), median [range]		3 [1–10]	
Courses of indomethacin, median [range]	–	2 [0–3]	
Surgical ligation, n (%)	–	10 (29)	
Duration (days) of hsPDA until closure, median [range]	–	3.5 [0–9]	
PNA at closure (days), median [range]	–	8 [2–14]	

PNA, postnatal age; PLDcort, preterm lung disease needing treatment with corticosteroids; $rScO_2$, regional cerebral oxygen saturation; severe PIVH, periventricular-intraventricular hemorrhage grade 3 or grade 4 according to Papile.

3.1. Long-term neurodevelopmental outcome

Results are shown in Table 2. Infants in the hsPDA group showed poorer motor performance scores compared to the NohsPDA group, which was most pronounced for the subdomain “aiming and catching”. Overall, infants with hsPDA had a higher incidence of poor motor outcome compared to the group without hsPDA. There were no relevant differences in the cognitive outcome scores between the two groups.

3.2. Multivariate regression analysis

MLR analysis revealed no significant associations between the independent variables and the total motor test score, as shown in Supplemental Table 2, including existence of hsPDA. However, for the specific subdomain “aiming and catching” there was a strong negative association between hsPDA and motor performance ($\beta = -16.69$; $p = 0.002$). PLDcort was also negatively related to this specific motor score

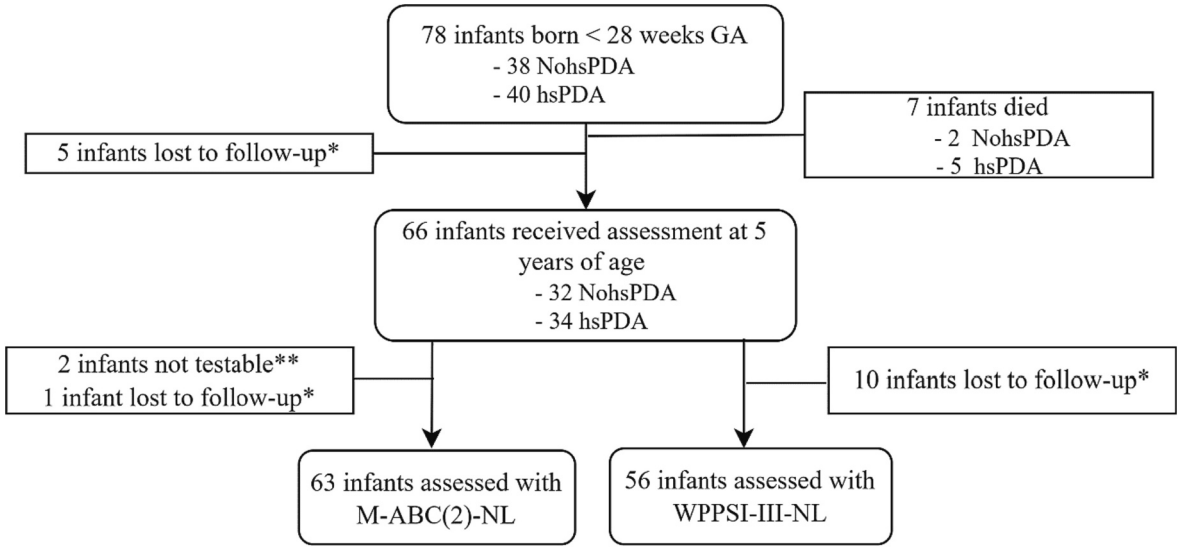

Fig. 1. Flowchart of inclusions and lost to follow-up.
*Lost to follow-up due to repeatedly no-shows, parental refusal for long-term follow-up or cognitive follow-up performed elsewhere; ** 2 infants were not testable due to behavioural problems.

Table 2
Neurodevelopmental outcome at 5 years of age.

	NohsPDA	hsPDA	*p* value
2A: Motor outcome, sub-scores of M-ABC(2)-NL	$n = 31$	n = 32	
Age at testing (months), mean ± SD	69.9 ± 3.2	70.3 ± 2.0	0.58
Percentile Score Manual Dexterity, median [IQR]	25.0 [9.0–37.0]	9.0 [5.0–34.0]	0.15
Percentile Score Aiming and Catching, median [IQR]	37.0 [25.0–50.0]	16.0 [5.0–25.0]	0.001
Percentile Score Balance, median [IQR]	37.0 [9.0–50.0]	20.5 [2.8–46.7]	0.17
Total Percentile Score, median [IQR]	16.0 [9.0–37.0]	5.0 [2.0–25.0]	0.02
Poor Motor Outcome[a], n (%)	7 (23)	17 (53)	0.01
2B: Cognitive outcome, sub-scores of WPPSI-III-NL	$n = 27$	$n = 29$	
Age at testing (months), mean ± SD	69.4 ± 5.3	71.2 ± 2.4	0.10
Verbal IQ, mean ± SD	95.7 ± 14.4	98.9 ± 13.1	0.38
Performance IQ, mean ± SD	100.9 ± 13.3	98.1 ± 12.4	0.41
Total IQ, mean ± SD	96.2 ± 13.5	97.3 ± 13.2	0.77
PSQ, mean ± SD	88.9 ± 13.8	94.0 ± 16.1	0.22
Less Favourable Cognitive Outcome[b], n (%)	5 (19)	6 (20)	0.94

[a] PS < 6 M-ABC(2)-NL.
[b] <-1SD WPPSI-III-NL. IQ, intelligence quotient; PSQ, processing speed quotient.

($\beta = -12.75$; $p = 0.03$). After excluding the group of surgically ligated infants this previously found associations persisted (see Supplemental Table 3).

MLR analysis for cognitive outcome showed a significant association between $rScO_2$ value and the different IQ scores. No other associations between the selected variables and cognitive outcome scores were detected. No association between hsPDA and cognitive outcome was found (see Supplemental Table 4). Results of the subanalysis, excluding hsPDA infants who received surgical ligation, are shown in Supplemental Table 5. The associations between $rScO_2$ value and total and performance IQ scores were not affected. However, verbal IQ was not related to the $rScO_2$ value in this subanalysis. Existence of hsPDA tended to be positively related to the subdomain "processing speed quotient".

3.3. Post hoc analysis

Post hoc analysis was performed on the subgroup of preterm infants with hsPDA. This analysis showed that surgical treatment was negatively associated with motor outcome ($\beta = -19.68$; $p = 0.02$). When excluding the group of four infants that received primary surgical ligation, this negative association did not persist (data not shown). Pre-closure $rScO_2$ was not significantly related to motor outcome. Prolonged persistence of hsPDA seemed related to the specific subdomain "aiming and catching", but failed to reach statistical significance ($\beta = -1.59$; $p = 0.07$; see Supplemental Table 6).

There were no associations between ductal surgery and duration of ductal patency with cognitive outcome scores. In this group of infants pre-closure $rScO_2$ was significantly related to performance IQ, but not to other cognitive outcome scores (Supplemental Table 7).

4. Discussion

Extremely preterm infants with hsPDA showed a suboptimal motor outcome at 5 years of age. This impaired motor performance might be explained by the fact that this group appeared to be sicker in general, with a lower GA and more severe PIVH [18]. Surprisingly, a strong negative relation persisted between infants with hsPDA and the specific motor subdomain "aiming and catching". Moreover, this potential association persisted after excluding the group of surgically ligated infants. In our study, we did not show any difference in overall cognitive performance at 5 years of age between the group infants with or without hsPDA. Although our study cohort was small, we still found potential relevant associations between hsPDA and neurodevelopmental outcome.

How can we explain the association between hsPDA and the subdomain "aiming and catching"? A previous study from our group, which included infants born <30 weeks GA, who underwent surgical ductal closure, showed an association between duration of hsPDA with suboptimal cerebellar growth and lower neurodevelopmental outcome scores at 2 years of corrected age [9]. Since the cerebellum has an important role in modulating motor functions, a reduced cerebellar volume could have contributed to this suboptimal motor performance [19,20]. Although our current post hoc analysis suggested a negative relation between longer hsPDA duration and this specific motor subdomain, this failed to reach statistical significance. A potential explanation is the small and more heterogeneous group of extremely preterm infants in our study. Moreover, during this study a proactive treatment strategy was still common, which resulted in a limited duration of hsPDA with a maximum of 14 days. This limited duration of hsPDA could have protected these group of infants. In our previously performed study, the group of infants with delayed surgical closure (>21 days of duration of hsPDA), had abnormally small cerebellar volumes and suboptimal neurodevelopmental outcome especially [9]. In agreement with this observations is the study performed by Cambonie et al. In this study they compared long-term neurodevelopmental outcome in a cohort who partly received early screening on day 3 of life with the intention to treat hsPDA at a preclinical stage. The early screening group did not show altered neurodevelopmental outcome at 5,5 years of age compared to the non-screening group. Slightly higher survival rates were found and also higher performance scores on two items of intelligence [21].

Another interesting finding in the current study was the potential negative effect of lower cerebral oxygen saturation on cognitive outcome. In MLR analysis, a less favourable cognitive outcome at 5 years of age was associated with lower rScO2 levels. Furthermore, the group of infants with hsPDA showed to have lower cerebral oxygen saturation before ductal closure compared to infants without hsPDA. However, in our study group this did not appear to affect overall cognitive performance at 5 years of age. Post hoc analysis showed a negative association between cerebral oxygen saturation and performance IQ in infants with hsPDA, but no relation was found with the other cognitive outcome scores.

A limitation of our study is the relatively small study cohort. Therefore, we could correct for a limited amount of variables. Since other factors could influence neurodevelopment outcome, it is critical to emphasize that we do not claim to present causality between hsPDA, ductal patency and poor neurodevelopmental outcome. Furthermore, a total of ten patients received surgical ligation in the hsPDA group, which could have negatively affected neurodevelopmental outcome. However, excluding this specific group, did not change the previously found associations.

During the study period, a proactive treatment strategy promoting ductal closure was common. Nowadays, a watchful waiting or conservative treatment strategy is increasingly accepted, and has been shown to be noninferior to medical treatment in terms of short-term outcomes [22]. However, the potential long-term effects of this change in treatment strategy, which result in a longer duration of ductal patency, has yet to be investigated. This small study suggests potential negative effects of delayed ductal closure on motor outcome. Moreover, low cerebral oxygen saturation levels were associated with long-term cognitive outcome. These findings emphasizes the necessity of further research to assess the safety of extended ductal patency.

5. Conclusion

Infants with a hsPDA tend to show an impaired motor outcome for the specific subdomain "aiming and catching" at 5 years of age.

Extended ductal patency might be a negatively contributing factor. Furthermore, impaired cognitive outcome is associated with lower cerebral oxygen saturation. Further research is warranted to confirm the safety of an expectant policy towards hsPDA.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2024.105953.

CRediT authorship contribution statement

Moniek S. Veldhuis: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Laura M.L. Dix:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Johannes M.P.J. Breur:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Willem B. de Vries:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Corine Koopman:** Investigation, Writing – review & editing. **Maria J.C. Eijsermans:** Investigation, Writing – review & editing. **Henriette F.N. Swanenburg de Veye:** Investigation, Writing – review & editing. **Mirella C. Molenschot:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Petra M.A. Lemmers:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Frank van Bel:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Daniel C. Vijlbrief:** Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Acknowledgments

We thank R. van de Vosse for his technical support. Furthermore, we would like to thank all families who took part in this study.

Statement of ethics

The institutional review board of the University Medical Center Utrecht decided that this study was exempt from the Medical Research Involving Human Subjects Act (16/320). Parental consent for the use of the patient data was obtained.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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