# Impact of neonatal patent ductus arteriosus treatment on neurodevelopment at 5 years in children born extremely preterm

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**Conclusion**

- Neonatal patent ductus arteriosus (PDA) treatment with non-steroidal anti-inflammatory drugs (NSAIDs) was not associated with adverse neurodevelopment at school age in extremely preterm (EPT) born children
- PDA surgery was associated with increased risk of cognitive and hearing impairment at school age
- Long term effects on neurodevelopment should be taken into account when assessing PDA treatment options

## Introduction

Optimal management of a hemodynamic significant PDA in EPT infants (born < 28 gestational weeks) is debated. PDA surgery has been associated with adverse neurodevelopment in toddlers but studies at school-age are scarce.

## Methods

A cohort study of 849 EPT born children from 11 European countries, born 2011-2012. 1671 infants were discharged from the neonatal ward and 1021 participated in 5 year follow-up. ww.epiceproject.eu

The exposures 1) no PDA treatment, 2) PDA treatment only with NSAID 3) all PDA surgery (+/- NSAID) were studied in relation to neurodevelopment outcomes at 5 years of age

- Cerebral palsy yes/no (parental questionnaire PQ)
- Any motor impairment (Movement ABC ≤16$^{th}$percentile)
- Any hearing impairment (PQ)
- Any vision Impairment (PQ)
- Any cognitive impairment (Wechsler Preschool and Primary Scale of Intelligence WPPSI, full-scale intelligent quotient (FSIQ) <85)

The risk of any impairment (mild-moderate-severe) was analyzed in a neonatal risk factor propensity score adjusted logistic regression model (in Table 2 the factors included in the propensity score are shown).

## Results

Table 1

| Characteristics of the infants born < 28 weeks by PDA treatment category* | Overall, N = 849 | No PDA treatment, N = 390 | NSAID treatment only, N = 321 | All surgical treatment,** N = 138 | p-value*** |
|---|---|---|---|---|---|
| Mothers´ with highest educational level, n (%) N=818 | 306 (37) | 132 (35) | 116 (38) | 58 (43) | 0.3 |
| Multiples, n (%) | 238 (28) | 103 (26) | 101 (31) | 34 (25) | 0.2 |
| Prolonged rupture of membranes >12 hours, n(%) | 214 (25) | 114 (29) | 67 (21) | 33 (24) | 0.037 |
| Any antenatal steroid treatment, n (%) | 750 (88) | 360 (92) | 269 (84) | 121 (88) | 0.003 |
| Female sex, n (%) | 406 (48) | 198 (51) | 152 (47) | 56 (41) | 0.12 |
| Gestational age, weeks, median (IQR) | 26.6 (25.6, 27.3) | 27.0 (26.1, 27.4) | 26.3 (25.4, 27.1) | 25.6 (24.9, 26.7) | <0.001 |
| Birthweight (gram), median (IQR) | 850 (726, 992) | 912 (776, 1,020) | 826 (716, 964) | 764 (668, 900) | <0.001 |
| Small for gestational age, n (%) | 135 (16) | 55 (14) | 56 (17) | 24 (17) | 0.4 |
| Surfactant doses ≥2 n (%) N=724 | 292 (34) | 103 (26) | 128 (40) | 61 (44) | <0.001 |
| Early neonatal infection (<72 hours of age), n (%) N=709 | 85 (12) | 39 (12) | 35 (13) | 11 (10) | 0.7 |
| IVH of grade III or higher, n (%) | 90 (11) | 40 (10) | 34 (11) | 16 (12) | >0.9 |
| Mechanical ventilation on day 1, n (%) | 679 (80) | 286 (73) | 269 (84) | 124 (90) | <0.001 |
| Late neonatal infection (>72h of age), n (%) | 483 (57) | 197 (51) | 185 (58) | 101 (73) | <0.001 |
| Total days on mechanical ventilation, median (IQR) | 11 (4, 25) | 6 (2, 16) | 12 (5, 22) | 26 (17, 39) | <0.001 |
| Systemic postnatal corticosteroids for BPD, n (%) | 207 (25) | 62 (16) | 83 (26) | 62 (45) | <0.001 |
| BPD at 36 weeks postmenstrual age, n (%) N=832 | 292 (34) | 103 (26) | 105 (33) | 84 (61) | <0.001 |
| Neonatal morbidity (IVH, NEC, BPD, ROP) at discharge, n (%) | 217 (26) | 77 (20) | 90 (28) | 50 (36) | <0.001 |

*Children having PDA treatment had their PDA diagnosed with echocardiography. The treatment decision was guided by local hospital guidelines in the different European regions.
** 31/138 children had PDA surgery without prior NSAID treatment
***p-value < 0.05 was considered significant. Overall comparison between PDA treatment categories was tested with Kruskal Wallis test and Chi-square test.

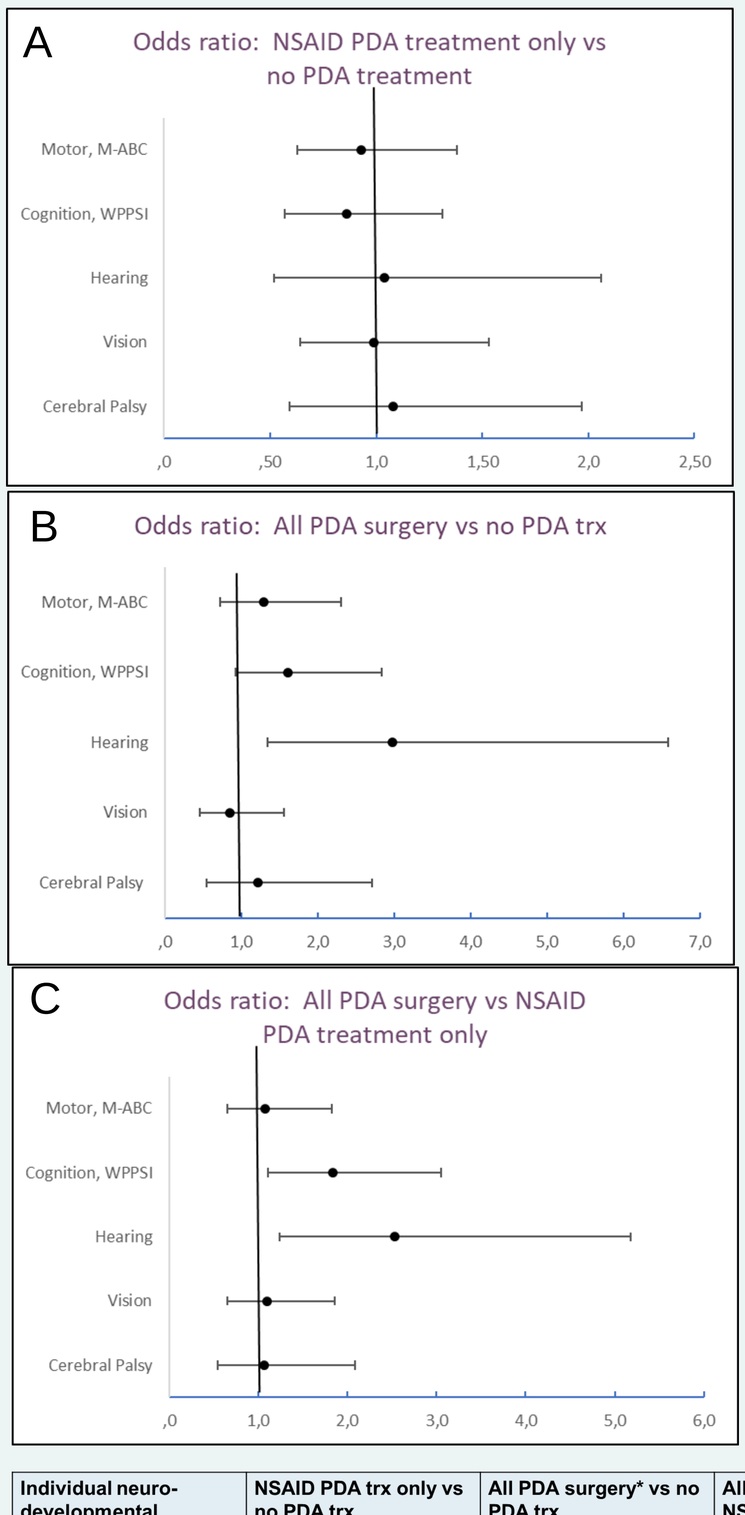


**Figure 1**

OR (odds ratio) for neurodevelopmental impairment did not increase in NSAID treated vs no PDA treatment (figure 1A).

The risk for hearing impairment was significantly increased in PDA surgery group vs no PDA treatment (figure 1B) and vs NSAID treatment (figure 1C).

The risk for cognitive impairment was increased in PDA surgery vs NSAID treatment group (figure 1C).

Adjustments were made for a neonatal risk factor propensity score (see table 2 for included factors) and mechanical ventilation on day 1.

| Individual neuro-developmental impairments | NSAID PDA trx only vs no PDA trx N=182 | All PDA surgery* vs no PDA trx N=67 | All PDA surgery* vs NSAID PDA trx only N=89 |
|---|---|---|---|
| Cerebral Palsy, OR (CI) | 1.16 (0.59-1.97) | 1.40 (0.46-4.30) | 1.25 (0.51-3.06) |
| Vision, OR (CI) | 1.14 (0.69-1.86) | 1.30 (0.59-2.88) | 1.11 (0.52-2.36) |
| Hearing, OR (CI) | 1.17 (0.53-2.61) | 2.49 (0.81-7.61) | 2.91 (0.99-8.55)† |
| Cognition, OR (CI) | 1.15 (0.71-1.87) | 1.20 (0.56-2.55) | **2.56 (1.28-5.14)**** |
| Motor, OR (CI) | 1.01 (0.64-1.57) | 1.54 (0.72-3.30) | 1.02 (0.53-1.97) |

The impairments were categorized as any (mild-moderate-severe) vs none, except for Cerebral Palsy (yes vs no). Within the entire cohort N=849, infants were matched 1:1, with a propensity score. The propensity score included multiple birth, mother's highest education level, region at birth, pre-eclampsia, prolonged rupture of membranes >12h, Cesarean delivery, spontaneous onset of delivery, antenatal steroid treatment (trx), gestational age, birthweight, sex, small for gestational age, infection as cause of delivery, early neonatal infection <72h of life, surfactant doses adminstered and IVH grade 3-4. *Limiting the analysis to children having both NSAID trx and PDA surgery (excluding 9/89 infants who had PDA surgery without prior NSAID trx) did not change the results. **significant with a p-value <0.05. † p=0.052

**Table 2**

A propensity score matched cohort sensitivity analysis was performed.

It confirmed the results for cognition but was borderline significant for hearing.

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