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ORIGINAL ARTICLE

Prophylactic low-dose paracetamol for ductal closure and neurodevelopmental outcome in very preterm infants

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Abstract

Aim: To investigate the direct effect of prophylactic low-dose paracetamol administration for ductal closure on neurodevelopmental outcome in very preterm infants who did not receive ibuprofen or surgical ligation for treatment of a patent ductus arteriosus.

Methods: Infants < 32 gestational weeks born 10/2014–12/2018 received prophylactic paracetamol (paracetamol group, $n = 216$); infants born 02/2011–09/2014 did not receive prophylactic paracetamol (control group, $n = 129$). Psychomotor (PDI) and mental (MDI) outcome were assessed using Bayley Scales of Infant Development at 12 and 24 months corrected age.

Results: Our analyses showed significant differences in PDI and MDI at age 12 months ($B = 7.8$ (95% CI 3.90–11.63), $p < 0.001$ and $B = 4.2$ (95% CI 0.81–7.63), $p = 0.016$). At age 12 months, the rate of psychomotor delay was lower in the paracetamol group (OR 2.22, 95% CI 1.28–3.94, $p = 0.004$). There was no significant difference between the rates of mental delay at any time-point. All group differences remained significant after adjustment for potential confounders (PDI 12 months $B = 7.8$ (95% CI 3.77–11.34), $p < 0.001$, MDI 12 months $B = 4.3$ (95% CI 0.79–7.45), $p = 0.013$, PDI < 85 12 months OR 2.65 (95% CI 1.44–4.87), $p = 0.002$).

Conclusion: We found no impairment of psychomotor and mental outcome at age 12 and 24 months in very preterm infants after prophylactic low-dose paracetamol administration.

KEYWORDS
neurodevelopmental outcome, patent ductus arteriosus, preterm infants, prophylactic paracetamol

Abbreviations: CPAP, continuous positive airway pressure; IQ, intelligence quotient; MDI, mental development index; MRI, magnetic resonance imaging; PDA, PAtent ductus arteriosus; PDI, psychomotor developmental index.

Michaela Höck and Maria Sappler equally contributed to this work.

1 | INTRODUCTION

Patent ductus arteriosus (PDA) is the most commonly diagnosed cardiovascular condition in preterm infants. PDA is associated with increased mortality and an increased incidence of short- and long-term morbidities such as chronic lung disease, intraventricular haemorrhage, necrotising enterocolitis or neurodevelopmental delay.[1] It is known that nonselective cyclooxygenase inhibitors (indomethacin and ibuprofen), that are conventionally used to induce ductal closure, may have multiple adverse effects.[2] Therefore, paracetamol has been propagated as an alternative drug with potentially fewer side effects.[3] At present, several studies provide evidence that the administration of low-dose prophylactic paracetamol is effective in terms of a lower rate of hemodynamically significant PDA. Relevant short-term adverse effects have not been observed so far.[4–9] However, information on long-term outcome of large cohorts of preterm infants exposed to paracetamol with the attempt to endorse early closure of the ductus arteriosus is lacking. Unfortunately, this is a matter of urgency since there are several reports linking paracetamol exposure during pregnancy or in the neonatal period with adverse outcomes including autism spectrum disorder, attention deficit hyperactivity disorder, lower IQ and language delay.[10–20]

In two previous studies, we found neither an adverse effect on amplitude-integrated electroencephalography signals during the neonatal period nor an impairment of microstructural maturation processes in the brain of very preterm infants (born at <32 gestational weeks) at term-equivalent age following prophylactic low-dose paracetamol administration to induce ductal closure.[21,22]

The aim of the current study was to investigate the direct effect of prophylactic low-dose paracetamol for closure of the ductus arteriosus, not mediated by subsequent medical or surgical treatment of a persistent ductus arteriosus, on neurodevelopmental outcomes at 12 and 24 months corrected age among very preterm infants who were treated and followed up at Innsbruck Medical University Hospital.

Key notes

- There exist conflicting data on potential negative effects of pre- and postnatal paracetamol exposure on neurobehavioral and cognitive outcomes.
- We investigated the effect of prophylactic low-dose paracetamol administration for ductal closure on neurodevelopmental outcome in a large cohort of very preterm infants.
- We did not observe any negative effect of prophylactic low-dose paracetamol administration on neurodevelopmental outcome until a corrected age of 24 months.

2 | MATERIALS AND METHODS

2.1 | Study design and population

This retrospective follow-up analysis of prospectively collected data was conducted at Innsbruck Medical University Hospital, which is the only neonatal intensive care unit in the geographical area (Tyrol, Austria). Very preterm infants, admitted to the neonatal intensive care unit of the Innsbruck Medical University Hospital between 1st January 2011 and 31st December 2018, were eligible for the study. Exclusion criteria were gestational age ≥ 32 weeks at birth, death, major congenital anomaly or congenital infection and being non-resident. The group of non-residents comprises infants from families who do not live in Tyrol, mainly tourists. These infants are transferred to a hospital in their native country as soon as possible. Naturally, these infants do not receive follow-up in our outpatient unit. Infants lost to follow-up (neither Bayley testing at 12 nor at 24 months corrected age) were not included in the final analysis. Furthermore, all preterm infants treated with ibuprofen and/or surgical ligation of the ductus were excluded from final analyses to investigate the specific effect of prophylactic low-dose paracetamol administration.

2.2 | Patient characteristics

Maternal and neonatal data were collected during the initial hospital stay including gestational age (completed weeks), birth weight (g), small for gestational age (defined as <10th centile for gestational age and sex using[23]), male sex, 5 min Apgar score < 7, multiple birth, maternal age < 23 years, antenatal steroid use (defined as at least one dose of intramuscular betamethasone at least 24 h prior to delivery), caesarean section, rupture of membranes >24 h before birth, early (<72 h) and late (>72 h) onset sepsis (defined as clinical signs of generalised infection and antibiotic therapy for >5 days), surfactant use, invasive ventilation, duration of continuous positive airway pressure (CPAP) respiratory support (days), chronic lung disease (defined as need for supplemental oxygen at day 28), achievement of full enteral feeding (days), necrotising enterocolitis[24] and retinopathy of prematurity grade 3 or 4. Brain injury was diagnosed by MRI and classified according to the method of Kidokoro et al[25] Kidokoro's current brain injury assessment covers three common injury patterns in preterm infants: intraventricular haemorrhage, white matter disease and cerebellar haemorrhage. All injury types are graded as grade 1 to grade 4 according to the degree of severity. High-grade injury (grade 3 or 4) in any category is defined as severe injury.

2.3 | Paracetamol administration

Prophylactic low-dose paracetamol administration was introduced into clinical practice in October 2014 for all preterm infants born at less than 32 gestational weeks. Therefore, infants born until September 2014 formed the control group and received no

preventive therapy and those born after September 2014 formed the paracetamol group and received intravenous paracetamol every 8 h (10 mg/kg birthweight[26]) started within the first 24 h without reference to the state of the ductus until ultrasound examination (after a minimum age of 72 h).

Paracetamol was routinely used during ophthalmologic examinations (in a dosage of 20 mg/kg orally) or as an analgesic drug in case of surgeries or other painful conditions. Every paracetamol administration in the control group and every additional administration after completing the course of prophylactic low-dose paracetamol in the paracetamol group was summed up under the term "additional paracetamol".

2.4 | Neurodevelopmental outcome

Follow-up visits at a corrected age of 12 and 24 months are part of our routine follow-up programme for all infants born at less than 32 gestational weeks. The follow-up visits include the quantitative assessment of motor and cognitive outcome by the use of Bayley Scales of Infant and Toddler Development. For infants born between June 2010 and December 2013 Bayley Scales of Infant Development, second edition (Bayley-II), and for infants born from January 2014 the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III), were used.[27] For Bayley-II, the only norms available were used (US norms). For Bayley-III, German norms were used.[28] The Bayley-II assesses psychomotor (PDI) and mental (MDI) developmental indices. To assess motor and mental outcome, Bayley-III evaluates motor, cognitive and language scales. We used the mean between the cognitive and language scale and equalised it with the former MDI as applied before.[29] The mean score is 100, a delayed neurodevelopmental outcome was defined as a score of <85.

2.5 | Statistical analyses

Continuous data are presented as median (IQR), and categorical data are summarised as numbers (frequencies; %). The Mann–Whitney U-test and the χ^2 test or Fisher's exact test were used to compare patient characteristics between the control group and the paracetamol group.

To assess the effect of paracetamol on neurodevelopmental outcome, linear regression analyses for continuous outcome variables and logistic regression analyses for binary outcome variables were conducted. In both, linear regression and logistic regression, Model 1 was adjusted for variables considered as potential confounders (gestational age at birth, small for gestational age, male sex, 5 min Apgar < 7, multiple birth, maternal age < 23 years, antenatal steroid use, caesarean section, and early onset sepsis). Model 2 was performed to assess the impact of variables with statistically significant differences in clinical characteristics of the study participants in the control group and the paracetamol group (gestational age, invasive ventilation, white matter disease, postmenstrual age at discharge).

Additional analyses of an enlarged population including infants who received medical/surgical treatment of the ductus arteriosus were performed. Model 1a, adjusted for potential confounders, included treatment with ibuprofen and/or surgical ligation, gestational age at birth, small for gestational age, male sex, 5 min Apgar < 7, multiple birth, maternal age < 23 years, antenatal steroid use, caesarean section and early onset sepsis. Model 2a, adjusted for differences in neonatal characteristics between the two groups, included treatment with ibuprofen and/or surgical ligation, male sex, invasive ventilation, white matter disease and postmenstrual age at discharge.

The level of significance for all statistical tests was set at a p value of <0.05. Data were analysed using IBM© SPSS© Statistics, version 25.0 for Windows.

3 | RESULTS

3.1 | Study population

During the study period, there were 541 infants born alive at a gestational age < 32 weeks. Thereof 249 infants are part of the control group and 292 infants of the paracetamol group. There were no significant differences in the mortality rates (4% (10/259) vs. 3% (9/292), $p = 0.556$) and the rates of major congenital anomaly or congenital infection (5% (13/249) vs. 2% (6/292), $p = 0.08$). The control group included 18 non-residents (7 German, 1 Dutch, 3 Italian, 7 Austrian from other federal states), whereas the paracetamol group included only eight non-residents (2 German, 1 Dutch, 1 Danish, 4 Austrian from other federal states) (7.2% (18/249) vs. 2.7% (8/292), $p = 0.02$). Thus 88.2% (477/541) of all infants were eligible for follow-up (83.5% (208/249) vs. 92.1% (269/292), $p = 0.002$). Infants without Bayley testing at either 12 or 24 months of age were not included in the final analysis (3.9% (8/208) vs. 5.2% (14/269), $p = 0.630$). Furthermore, we excluded all infants treated with ibuprofen and/or surgical ligation of the ductus (35.5% (71/200) vs. 15.3% (39/255), $p < 0.0001$). Finally, total of 345 infants with a median gestational age of 30.3 (28.8; 31.4) weeks were included in the study ($n = 129$ in the control group and $n = 216$ in the paracetamol group). The details are shown in Figure 1.

3.2 | Patient characteristics

Overall, a similar distribution of study-relevant clinical parameters was found in both groups. Infants in the paracetamol group were born at a lower median gestational age than infants in the control group ($p = 0.023$). They less often needed invasive ventilation ($p = 0.026$), but were longer on CPAP ($p = 0.011$). Infants in the paracetamol group were more often diagnosed with white matter disease grade 1 ($p = 0.024$). There was no difference in the rate of any other type/grade of brain injury detected by MRI at term-equivalent age. The postmenstrual age at discharge was significantly lower in the paracetamol group ($p = 0.007$). Detailed maternal and neonatal data are shown in Table 1.

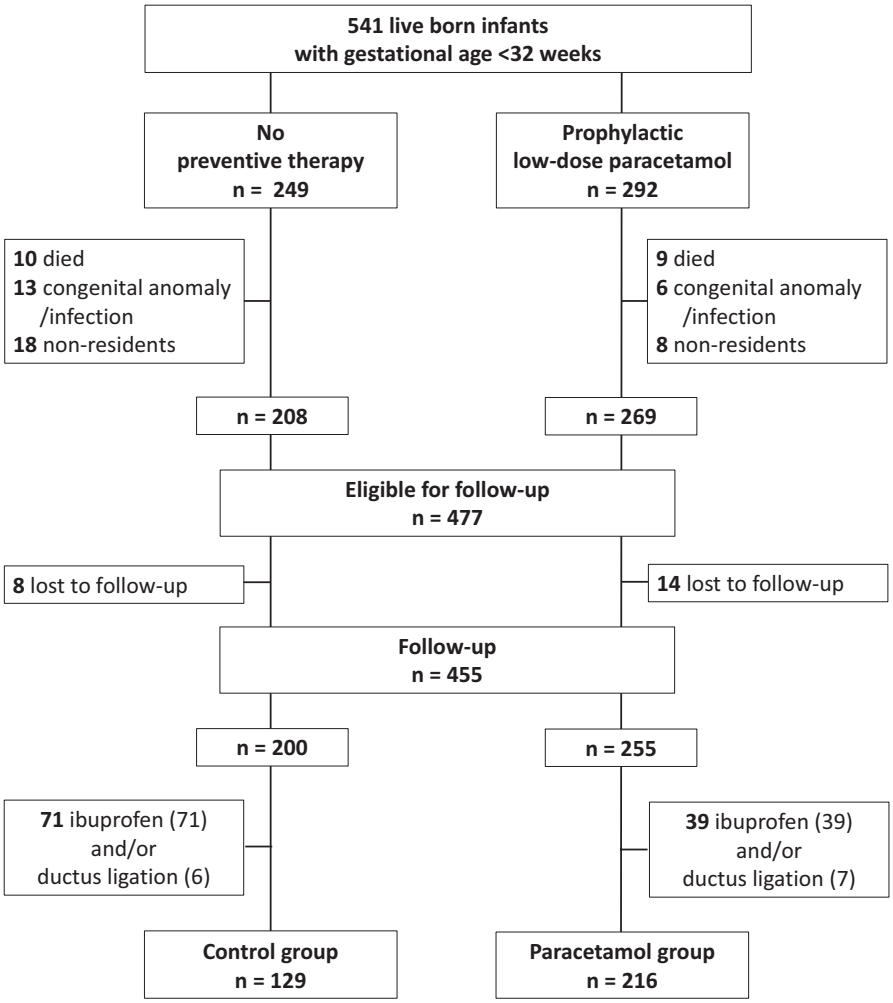

FIGURE 1 Flowchart of the inclusion and exclusion procedures.

3.3 | Paracetamol administration

The median cumulative dose of prophylactic paracetamol was 107 (90; 130) mg/kg. The median amount of paracetamol administered in addition to the prophylactic paracetamol at any time until discharge was 22 (20; 60) mg/kg. This amount did not differ from the control group (20 (20; 40) mg/kg, $p = 0.069$).

3.4 | Neurodevelopmental outcome

Comparison of neurodevelopmental outcome of infants in the control group with infants in the paracetamol group is available as Table 2: These analyses showed a higher median PDI at a corrected age of 12 and 24 months in the paracetamol group ($p < 0.0001$ and $p = 0.044$). At a corrected age of 12 months, the rate of psychomotor delay was lower in the paracetamol group ($p = 0.004$). At a corrected age of 24 months, there was no significant difference in the rate of neurodevelopmental delay. Regarding mental outcome, we observed a significantly higher median MDI at a corrected age of 12 months in the paracetamol group ($p = 0.009$). There was no significant difference between either median MDI at corrected age of 24 months or between the rates of mental delay at any time-point.

Linear and logistic regression analyses of the effect of prophylactic low-dose paracetamol on neurodevelopmental outcome are shown in Table 3.

The unadjusted model showed significant effects of prophylactic low-dose paracetamol on neurodevelopmental outcome in PDI ($B = 7.8$ (95% CI 3.90–11.63), $p < 0.001$) and MDI at a corrected age of 12 months ($B = 4.2$ (95% CI 0.81–7.63), $p = 0.016$). At a corrected age of 12 months, the rate of psychomotor delay was lower in the paracetamol group (OR 2.22, 95% CI 1.28–3.94, $p = 0.004$). There was no significant effect on the rate of mental delay at any time-point.

Model 1 (adjusted for potential confounders) showed that the effect remained significant (PDI 12 months: $B = 7.8$ (95% CI 3.77–11.34), $p < 0.001$, MDI 12 months: $B = 4.3$ (95% CI 0.79–7.45), $p = 0.013$ and PDI < 85 12 months: OR 2.65, 95% CI 1.44–4.87, $p = 0.002$).

Model 2 (adjusted for significant differences in neonatal characteristics) showed that the difference in median PDI and MDI at the corrected age of 12 months (PDI 12 months $B = 7.8$ (95% CI 3.70–11.86), $p < 0.001$; MDI 12 months $B = 2.5$ (95% CI 0.03–7.44, $p = 0.048$) and the rate of psychomotor delay remained significant (OR 2.39, 95% CI 1.26–4.54, $p = 0.008$)).

TABLE 1 Maternal and neonatal demographic and clinical characteristics of babies born at <32 gestational weeks to mothers resident in the Tyrol region, Austria, admitted to neonatal intensive care unit at the Medical University of Innsbruck between January 2011 and December 2018 before (up to September 2014 – control group) and after (from October 2014 – paracetamol group) introduction of routine prophylactic paracetamol ($n = 345$).

	Control group ($n = 129$)	Paracetamol group ($n = 216$)	
	median (IQR) or *n* (%)		*p*-Value
Gestational age (weeks)	30.7 (29.0; 31.5)	30.0 (28.6; 31.3)	**0.023**
Birth weight (g)	1372 ± 407	1301 ± 354	0.077
Small for gestational age	11 (8.5%)	14 (6.5%)	0.478
Male sex	64 (49.6%)	124 (57.4%)	0.159
Gestational age < 28 weeks	18 (14.0%)	39 (18.1%)	0.321
Apgar Score 5 min < 7	12 (9.3%)	12 (5.7%)	0.216
Multiple birth	52 (40.3%)	85 (39.4%)	0.860
Maternal age < 23 years	9 (7.0%)	10 (4.7%)	0.378
Antenatal steroid use	122 (95.3%)	200 (92.6%)	0.319
Ceasarean section	119 (92.2%)	197 (94.7%)	0.363
Rupture of membranes > 24 h	23 (18.4%)	48 (23.3%)	0.292
Early onset sepsis	5 (3.9%)	15 (6.9%)	0.251
Late onset sepsis	15 (11.6%)	20 (9.3%)	0.481
Surfactant use	94 (72.9%)	161 (75.9%)	0.526
Invasive ventilation	74 (58.3%)	99 (45.8%)	**0.026**
CPAP duration (days)	4 (2; 8.5)	7 (3; 19)	**0.011**
Chronic lung disease	23 (17.8%)	39 (18.1%)	0.958
Full enteral feeding (days)	10 (8:12)	10 (9:13)	0.053
Necrotising enterocolitis	3 (2.3%)	5 (2.5%)	0.937
Retinopathy of prematurity grade 3 or 4	6 (4.7%)	3 (1.5%)	0.081
Intraventricular haemorrhage[a]	13 (10.6%)	34 (16.7%)	0.128
White matter disease[a]	9 (7.3%)	41 (20.1%)	**0.002**
Grade 1	2 (1.6%)	15 (7.4%)	**0.024**
Grade 2	6 (4.9%)	16 (7.8%)	0.300
Grade 3	0 (0%)	3 (1.5%)	0.177
Grade 4	1 (0.8%)	7 (3.4%)	0.138
Cerebellar haemorrhage[a]	7 (5.7%)	20 (9.8%)	0.191
Postmenstrual age at discharge (weeks)	36.9 (36.3; 38.2)	36.5 (36.0; 37.72)	**0.007**
Cumulative prophylactic paracetamol (mg/kg)	0	107 (90; 130)	
Cumulative additional paracetamol (mg/kg)	20 (20; 40)	22 (20; 60)	0.069

Note: Tested via Mann–Whitney U-test and the χ^2 test or Fisher's exact test. *p* Values in bold indicate $p < 0.05$.

[a]Detected by MRI at term equivalent age.

3.5 | Additional analyses in an enlarged population including all infants eligible for follow-up (before exclusion of infants treated with ibuprofen and/or surgical ligation of the ductus)

A comparison of patient characteristics between all infants eligible for follow-up before exclusion of infants treated with ibuprofen and/or surgical ligation of the ductus ($n = 208$ in the control group and $n = 269$ in the paracetamol group) is shown as Table S1.

A comparison of neurodevelopmental outcome of infants in the control group with infants in the paracetamol group, including all infants eligible for follow-up before exclusion of infants treated with ibuprofen and/or surgical ligation of the ductus, is shown as Table S2. The results were similar to the initial findings with the exception that there was a trend for higher median MDI ($p = 0.052$) and a lower rate of mental delay ($p = 0.031$) at a corrected age of 24 months in the paracetamol group.

Linear and logistic regression analyses of the effect of prophylactic low-dose paracetamol on neurodevelopmental outcome are

TABLE 2 Neurodevelopmental outcome of babies born at <32 gestational weeks to mothers resident in the Tyrol region, Austria, admitted to neonatal intensive care unit at the Medical University of Innsbruck between January 2011 and December 2018 before (up to September 2014 – control group) and after (from October 2014 – paracetamol group) introduction of routine prophylactic paracetamol.

	Control group ($n=129$)	Paracetamol group ($n=216$)	
	median (IQR) or *n* (%)		*p*-Value
12 months			
PDI	90 (81; 103)	103 (92; 109)	**<0.0001**
PDI < 85	34/124 (27.4%)	31/213 (14.6%)	**0.006**
24 months			
PDI	100 (92; 110)	106 (96; 113)	**0.044**
PDI < 85	13/112 (11.6%)	24/185 (13.0%)	0.857
12 months			
MDI	102 (94; 109)	105 (95; 115)	**0.009**
MDI < 85	8/121 (6.6%)	11/212 (5.2%)	0.629
24 months			
MDI	106 (90; 114)	105 (95; 115)	0.428
MDI < 85	16/110 (14.5%)	18/184 (9.8%)	0.259

Note: Tested via Mann–Whitney U-test and the χ^2 test or Fisher's exact test. *p* values in bold indicate $p<0.05$. The differing sample sizes for each analysis are explained by pairwise deletion of missing data.

Abbreviations: MDI, mental development index; PDI, psychomotor developmental index.

shown in Table S3. The results were similar to the initial findings with the exception that univariate analysis showed a significant difference for PDI at a corrected age of 24 months ($B=4.2$ (95% CI 0.91–7.57), $p=0.013$). Model 1a (adjusted for potential confounders) showed that this difference ($B=3.5$ (95% CI 0.10–6.96), $p=0.044$) remained significant, but statistical significance was lost in model 2a (adjusted for significant differences in neonatal characteristics).

4 | DISCUSSION

In this study including 345 closely monitored very preterm infants, we did not find any negative effect of prophylactic low-dose paracetamol administered to endorse early closure of the ductus arteriosus on neurodevelopmental outcome at a corrected age of 12 and 24 months. This is in so far an important observation as there are studies connecting perinatal paracetamol exposure with adverse behavioural and cognitive development.[12–20] Several studies report an association of intrauterine exposure to paracetamol with autism spectrum disorder and attention deficit hyperactivity disorder. Furthermore, there are studies linking prenatal use of paracetamol with lower IQ and language delay in exposed infants.[12,17] The reliability of these findings is limited by the fact that most studies concerning prenatal paracetamol use are based on self-reported data.

An analysis of six European population-based cohorts including 73.000 infants also assessed pre- and postnatal paracetamol exposure through maternal interviews and found no association of postnatal paracetamol exposure with autism spectrum disorder or attention deficit hyperactivity disorder[18] In mice, it has been shown that postnatal paracetamol administration affected cognitive functioning and adult responsiveness to paracetamol.[19] Furthermore, Bauer et al. indicated that early postnatal paracetamol use is correlated with autism spectrum disorder in male children in the United States.[20] Although the authors emphasised that they cannot provide strong evidence of causality, it has to be mentioned that in this study the circumcision rate was used as a surrogate for postnatal paracetamol exposure and data on actual paracetamol use do not exist in this cohort. Knowledge on the effect of postnatal paracetamol in the context of prematurity is restricted to data from 44 Finnish infants. This study did not provide any evidence of an increased risk of neurodevelopmental problems until the age of 5 years in this small cohort.[30,31]

In our cohort of very preterm infants, we did not find any negative effect of prophylactic low-dose paracetamol administration on neurodevelopmental outcome at a corrected age of 12 and 24 months. In our previous work, we have already shown that the rate of PDA requiring treatment was lower in the paracetamol group.[7] Thus, the exclusion of all preterm infants treated with ibuprofen or surgical ligation to investigate the specific effect of prophylactic low-dose paracetamol administration results in a higher number of immature infants in the paracetamol group than in the control group and these infants have a higher intrinsic risk for psychomotor or cognitive delay. Bearing this in mind, it is remarkable that we did not find any negative effect on neurodevelopmental outcome in infants who received prophylactic low-dose paracetamol. Furthermore, the findings of the current study are supported by our previous work where we did not observe any impairment in microstructural and functional brain maturation after prophylactic low-dose administration in the same cohort, but in some aspects even a maturational advance.[21,22]

So far, it has not been demonstrated that the prophylactic low-dose paracetamol administration enhances long-term outcomes of preterm infants. A potential advantageous effect on brain maturation and neurodevelopmental outcome in the paracetamol group could be explained via an improved cerebral blood flow after an earlier closure of the ductus arteriosus. Furthermore, pain-related stress has been associated with alterations in developmental outcomes of preterm infants.[32] Thus, another explanation for a potential enhancing effect of paracetamol on brain development may be based on the analgesic effect of this drug. Since standardised pain assessment was not included in our study, this hypothesis cannot be clarified by now.

4.1 | Strengths and limitations

The retrospective study design with a historical cohort as control group is the main limitation of the study and potential confounding

TABLE 3 Evaluation of the effect of prophylactic low-dose paracetamol on neurodevelopmental outcome of babies born at <32 gestational weeks to mothers resident in the Tyrol region, Austria, admitted to neonatal intensive care unit at the Medical University of Innsbruck between January 2011 and December 2018 before (up to September 2014 – control group) and after (from October 2014 – paracetamol group) introduction of routine prophylactic paracetamol.

	Unadjusted model				Model 1[a]				Model[b]			
		*R^2 or				*Corrected R^2 or				*Corrected R^2 or		
	B	**OR	95% CI	*p* Value	*B*	**OR	95% CI	*p* Value	*B*	**OR	95% CI	*p* Value
12 months												
PDI[c]	7.8	*0.05	3.90 to 11.63	**<0.001**	7.8	*0.10	3.77–11.34	**<0.001**	7.8	*0.11	3.70–11.86	**<0.001**
PDI < 85[d]	–	**2.22	1.28 to 3.84	**0.004**	–	**2.65	1.44–4.87	**0.002**	–	**2.39	1.26–4.54	**0.008**
24 months												
PDI[c]	2.5	*0.01	−1.46 to 6.36	0.218	–	–	–	–	–	–	–	–
PDI < 85[d]	–	**0.88	0.43 to 1.81	0.730	–	–	–	–	–	–	–	–
12 months												
MDI[c]	4.2	*0.02	0.81 to 7.63	**0.016**	4.3	*0.08	0.79–7.45	**0.013**	2.5	*0.03	0.03–7.44	**0.048**
MDI < 85[d]	–	**1.28	0.50 to 3.28	0.604	–	–	–	–	–	–	–	–
24 months												
MDI[c]	2.5	*0.00	−1.92 to 6.84	0.270	–	–	–	–	–	–	–	–
MDI < 85[d]	–	**1.57	0.77 to 3.22	0.219	–	–	–	–	–	–	–	–

Note: Bold indicates statistical significant value ($p < 0.05$).

Abbreviations: B, beta regression coefficient; CI, confidence interval; MDI, mental development index; OR, odds ratio; PDI, psychomotor developmental index, Rb coefficient of determination.

[a]Model 1 adjusted for potential confounders (gestational age, birth weight, small for gestational age, male sex, 5 min Apgar < 7, multiple birth, maternal age < 23 years, antenatal steroid use, caesarean section and early onset sepsis).

[b]Model 2 adjusted for significant differences in neonatal characteristics (gestational age, invasive ventilation, white matter disease, postmenstrual age at discharge).

[c]Tested via linear regression.

[d]Tested via logistic regression. Values listed for the variable prophylactic low-dose paracetamol yes (coded 1)/no (coded 0).

cannot be excluded. However, there are neither differences in the mortality rate nor in the follow-up rate. There were no changes in the geographical coverage or healthcare provision during the two eras and the staff as well as our therapy standards remained largely unchanged during the study period. Both groups are representative of patients in a high-level neonatal intensive care unit. Furthermore, there is a low rate of infants lost to follow-up. Regarding follow-up, it has to be mentioned as limitation that Bayley-II was updated to Bayley-III within the study period. We use Bayley-III German norms as a population-specific norm to cope with this issue best possible. In contrast to US norms for Bayley-III, which are known to underestimate developmental delay, it has been shown that very preterm infants achieved significantly lower scores when using German as compared to the US norms.[33,34] So far, there is no study available comparing Bayley-II with Bayley-III German norms. In our own analysis including 759 infants from 2007 to 2018, we did not find a higher rate of infants with delay using Bayley-II versus Bayley-III German norms (Hammerl et al., publication in preparation, unpublished data).

4.2 | Conclusions

In summary, there exist conflicting data on potential negative effects of pre- and postnatal paracetamol exposure. Upon closer examination, current studies do not provide definite evidence that (low-dose, short-term) postnatal paracetamol exposure is causally related to either neurobehavioral or cognitive disorders. Furthermore, until now, there is no information on cerebral correlates of the above described phenomenon of paracetamol induced neurocognitive and behavioural alterations in immature infants. In this study, we did not assess behavioural problems. Thus, specific assessment for autism spectrum disorder and attention deficit hyperactivity disorder as well as the quantification of cognitive abilities at age 5 years will be essential for our comprehensive work-up on the effect of prophylactic low-dose paracetamol administration on the immature brain.

In our previous studies, we found no impairment of functional and microstructural maturation processes in the brain of very preterm infants following prophylactic low-dose paracetamol administration.[21,22] For the current study, we can report that we did not observe any negative effect of prophylactic low-dose paracetamol administration neurodevelopmental outcome until a corrected age of 24 months in our cohort including 345 closely monitored very preterm infants. However, more data are needed before recommending use of this treatment strategy more generally.

AUTHOR CONTRIBUTIONS

Mi.H., V.N. and U.K.-K. initiated and designed the study. V.N., Mi.H., M.H., M.S. and U.P.-P. participated in data collection. U.P.-P. evaluated the Bayley Scores. J.-P. N. and M.S. planned and conducted the statistical analyses. M.S., Mi.H. and V.N. drafted the manuscript and reviewed the literature. All authors participated in data interpretation. V.N., M.S. and J.-P. N. revised the manuscript. E.G. and U.K.-K. supervised the study. All authors approved the final version for publication.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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