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Prophylactic Low-Dose Paracetamol Administration for Ductal Closure and Microstructural Brain Development in Preterm Infants

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Keywords
Patent ductus arteriosus · Preterm infants · Neurodevelopmental outcome · Diffusion tensor imaging · Microstructural brain development

Abstract
Introduction: Prophylactic low-dose paracetamol administration is used to induce closure of the ductus arteriosus. Effects on the neurological outcome in preterm infants remain unknown. We compared microstructural brain development in very preterm infants with and without exposure to prophylactic paracetamol by using MR-based diffusion tensor imaging. ***Materials and Methods:*** Infants aged <32 gestational weeks born between October 2014 and December 2018 received prophylactic paracetamol (10 mg/kg intravenously every 8 h until echocardiography after at least 72 h) and form the paracetamol group; infants born between February 2011 and September 2014 form the control group. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) at term-equivalent age were measured in 14 defined cerebral regions and compared between the groups. ***Results:*** Included in the study were 340 infants, of whom 217 received prophylactic paracetamol, and 123 formed the control group. The paracetamol group showed significantly higher FA values and lower ADC values in the splenium of the corpus callosum, as well as higher FA values in the pons bilaterally, the left middle cerebellar peduncle, the right occipital white matter, and the right posterior limb of the internal capsule ($p \leq 0.02$). ***Conclusion:*** The perceived safety of prenatal paracetamol exposure has been questioned in recent years. We found no impairment on microstructural maturation processes in the brain of preterm infants at term-equivalent age following early paracetamol administration. The clinical relevance of these imaging findings has to be determined in long-term follow-up studies on neurodevelopmental outcome.

Introduction

Patent ductus arteriosus (PDA) is a common condition in preterm infants. It is linked to increased mortality and multiple, harmful short- and long-term outcomes. However, it has been shown that screening for and ther-

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apy of PDA might be associated with decreased mortality and morbidity in some infants. There is also evidence that the established treatment options carry substantial risks that may outweigh benefits [1, 2]. Currently, we are without a means to identify which subset of preterm infants is most likely to benefit from PDA closure. In this setting, paracetamol has gained attention as a pharmacological option to induce early closure of the ductus arteriosus with the idea that this drug might have fewer side effects than do COX inhibitors. Recently, several studies showed a lower incidence of hemodynamically significant PDA after early paracetamol administration [3–7]. The therapy appears to be safe, causing fewer short-term side effects, particularly lower rates of gastrointestinal and renal complications than does ibuprofen or indomethacin [8, 9]. However, follow-up data on preterm infants exposed to prophylactic paracetamol are limited to short-term outcomes. In addition, there are studies linking prenatal paracetamol exposure to adverse neurodevelopmental outcomes [10]. A topic which is controversially discussed among pediatricians [11, 12].

The aim of the current study was to investigate the effect of prophylactic low-dose paracetamol administration on brain development in a large cohort of preterm infants. We compared microstructural brain development in very preterm infants with and without exposure to prophylactic paracetamol by using MR-based diffusion tensor imaging (DTI) at term-equivalent age.

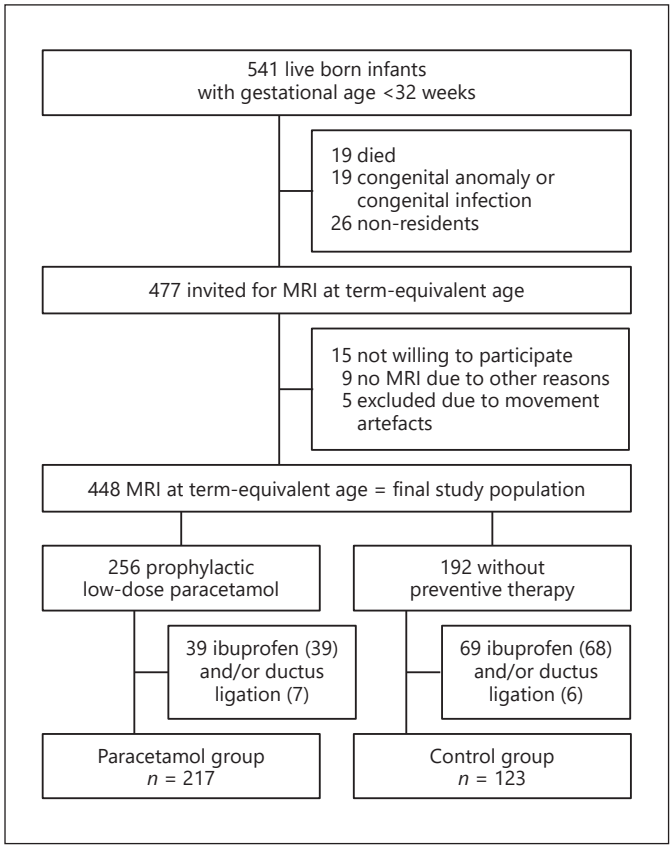

Fig. 1. Flowchart of the inclusion and exclusion procedures.

Materials and Methods

Study Population and Study Design

The study was conducted as a retrospective analysis of prospectively collected data. All infants born at less than 32 gestational weeks between February 2011 and December 2018 at Innsbruck Medical University Hospital (Austria) were enrolled. To investigate the specific effect of prophylactic low-dose paracetamol administration, we excluded all preterm infants treated with ibuprofen or surgical ligation. The detailed inclusion and exclusion procedures are shown in Figure 1. Maternal and neonatal data were collected during the hospital stay as described in our previous paper [13].

Paracetamol Administration

Prophylactic low-dose paracetamol administration was introduced in October 2014 for all infants born at less than 32 gestational weeks. Thus, infants born until September 2014 were included in the control group and those born after September 2014 in the paracetamol group. The latter received prophylactic paracetamol (Perfalgan©, Bristol-Meyers Squibb; 10 mg/kg birthweight intravenously, every 8 h) within the first day without reference to the state of the ductus until echocardiography after at least 72 h. Those in the control group received no preventive therapy. Each administration in the control group and the administrations in addition to the prophylaxis in the paracetamol group are summarized and referred to as "additional paracetamol". Throughout the study period, paracetamol was routinely used during ophthalmologic examinations in a dosage of 20 mg/kg orally. Furthermore, paracetamol was administered as an analgesic drug in case of surgeries or other painful conditions. All these prescriptions are summed up under the term "additional paracetamol".

MRI Procedure and Imaging Details

Cerebral MRI at term-equivalent age is part of our routine follow-up program for all preterm infants born at less than 32 gestational weeks [14]. Images were acquired at the local Department of Neuroradiology with a Siemens 3.0 Tesla scanner using the following protocol for diffusion-weighted images: axial images covering the whole brain (matrix 160 × 160; *b* value = 0 and 1,000 s/mm^2; DTI sequence with 20 directions repeated twice; TE/TR = 101/6,600 ms). In 2017, the scanner model MAGNETOM Verio was replaced by Skyra (both Siemens, Erlangen, Germany). To exclude the exchange of the scanner model as a potential confounder, the scanner type was included in the multivariate logistic regression analysis.

Cerebral injury was graded according to Kidokoro et al. [15]. The images were evaluated by two operators blinded to the clinical data. Consensus was reached by discussion.

We measured fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values using IMPAX© EE R20 XVIII

Table 1. Maternal and neonatal characteristics

Variable	Paracetamol group (n = 217)	Control group (n = 123)	p value
Antenatal steroid use	200 (92.2)	116 (95.1)	0.306
Premature rupture of membranes >24 h	47 (22.2)	21 (17.6)	0.328
Caesarean section	203 (94.9)	114 (92.7)	0.415
Multiple birth	83 (38.2)	49 (39.8)	0.773
Gestational age at birth, weeks	29.9 (28.5–31.2)	30.7 (29.0–31.4)	**0.012**
Gestational age <28 weeks	39 (18.0)	17 (13.8)	0.321
Birthweight, grams	1,300 (1,035–1,560)	1,370 (1,080–1,700)	0.093
Small for gestational age	13 (6.0)	11 (8.9)	0.307
Male sex	126 (58.1)	61 (49.6)	0.131
Apgar score 5 min <7	13 (6.0)	10 (8.1)	0.464
Surfactant use	159 (74.0)	89 (72.4)	0.749
Invasive ventilation	98 (45.0)	69 (57.0)	**0.033**
Full enteral feeding, days	10.0 (9.0–13.0)	10.0 (8.0–12.0)	0.084
Early-onset sepsis	15 (6.9)	4 (3.3)	0.168
Late-onset sepsis	21 (9.7)	14 (11.4)	0.619
Bronchopulmonary dysplasia	38 (17.5)	23 (18.7)	0.784
Necrotizing enterocolitis	6 (2.9)	3 (2.4)	0.815
Retinopathy of prematurity grade 3–4	3 (1.5)	6 (4.9)	0.066
Postmenstrual age at discharge, weeks	36.4 (36.0–37.7)	36.9 (36.3–38.0)	**0.005**

Data are presented as n (%) or median (IQR).

(Agfa HealthCare N.V., Mortsel, Belgium). FA values are unitless, and the unit 10^{-3} mm^2/s applies to all specified ADC values. FA and ADC values were measured bilaterally in the centrum semiovale, in the posterior limb of the internal capsule, the occipital white matter (WM), the middle cerebellar peduncles (MCPs), the cerebellum, and in the genu and splenium of the corpus callosum as described by Pogribna, Jeong, Nijman, and Brouwer [16–19]. Regions of interest for the pons were chosen at the level of the MCPs with a central circle of 2 mm^2 area. Regions were manually positioned on the FA map and copied to the ADC map as described in a previous study [20]. To validate our data, 20 infants selected at random were analyzed by two independent observers. For these 20 infants, measurements were repeated after a time interval of at least 24 h. We achieved intraclass correlation coefficients for inter- and intrarater reliability between 0.68 and 0.99. For the current study, we used the measurements taken by one investigator.

Statistical Analysis

Continuous data are presented as median (IQR), and categorical data are summarized as numbers (frequencies; %). The Mann-Whitney U test and the χ^2 test were used where appropriate. Multivariate logistic regression analysis including all significant differences in patient characteristics (gestational age, invasive ventilation, postmenstrual age at discharge, and WM disease [WMD] I°) as well as the MRI scanner type was used to account for potential confounders. A p value <0.05 was considered statistically significant. Data analysis was performed using SPSS, version 24.0 for Windows (IBM Corp., Armonk, NY, USA). Boxplots were generated using the software R, version 3.6.3.

Results

Study Population

A total of 340 preterm infants between 24 + 0 and 31 + 6 gestational weeks were included, of whom 217 (63.8%) patients formed the paracetamol group and 123 (36.2%) patients the control group. Maternal characteristics were equally distributed among the groups. Infants in the paracetamol group were born at a lower median gestational age than infants in the control group (29.9 vs. 30.7 weeks; p = 0.012). There was a difference in the frequency of invasive ventilation, with the paracetamol group being less often ventilated (98 [45%] vs. 69 [57%]; p = 0.030). Infants in the paracetamol group were discharged at a lower median postmenstrual age than were the controls (36.4 vs. 36.9 weeks; p = 0.005). There was no significant difference in any other neonatal characteristic. Table 1 summarizes patients' characteristics.

Paracetamol Administration

The paracetamol group received a median of total 109 (90–130) mg/kg of paracetamol as prophylaxis. The median amount of paracetamol administered in addition to the prophylactic paracetamol at any time during the hos-

Table 2. MRI data

Variable	Paracetamol group (n = 217)	Control group (n = 123)	p value
Postmenstrual age at MRI, weeks	40.6 (40.1–40.7)	40.6 (40.1–41.0)	0.073
Intraventricular hemorrhage	34 (15.7)	12 (9.8)	0.122
Grade III/IV	4 (1.9)	1 (0.8)	0.446
Cerebellar hemorrhage	20 (9.3)	7 (5.7)	0.243
Grade III/IV	3 (1.4)	0 (0)	0.189
WMD	42 (19.4)	9 (7.3)	**0.003**
Grade I	15 (6.9)	2 (1.6)	**0.031**
Grade II	17 (7.9)	6 (4.9)	0.292
Grade III	3 (1.4)	0 (0)	0.189
Grade IV	7 (3.2)	1 (0.8)	0.157

Data are presented as *n* (%) or median (IQR).

pital stay was 21 (20–60) mg/kg and did not differ significantly from the control group receiving 21 (20–40) mg/kg (p = 0.155).

MRI at Term-Equivalent Age

The patients underwent cerebral MRI at a median of 40.6 weeks. WMD was more often diagnosed in infants in the paracetamol group (p = 0.003). Detailed analyses regarding the severity of WMD showed a higher frequency of grade I lesions in the paracetamol group (p = 0.031, Table 2).

DTI Measurements

Comparison of the two groups showed no significant differences in FA values in 7 of the 14 regions of interest or in ADC values in 12 of the 14 regions of interest. In the paracetamol group as compared to the control group, there were significantly higher FA values in the splenium of the corpus callosum (0.68 [0.64–0.72] vs. 0.66 [0.60–0.70]; p = 0.007), the pons bilaterally (right 0.33 [0.30–0.36] vs. 0.31 [0.26–0.33]; left 0.35 [0.31–0.37] vs. 0.30 [0.27–0.34]; p < 0.001), the MCPs bilaterally (right 0.59 [0.56–0.63] vs. 0.57 [0.54–0.61]; p = 0.003; left 0.60 [0.56–0.64] vs. 0.57 [0.56–0.64]; p < 0.001), the right posterior limb of the internal capsule (0.64 [0.62–0.66] vs. 0.62 [0.60–0.65]; p < 0.001), and the right occipital WM (0.34 [0.30–0.40] vs. 0.32 [0.28–0.37]; p = 0.005) and significantly lower ADC values in the splenium of the corpus callosum (1.11 [1.06–1.19] vs. 1.15 [1.09–1.23]; p = 0.01). ADC values in the left posterior limb of the internal capsule were higher in the paracetamol group than in the control group (0.98 [0.95–1.01] vs. 0.97 [0.93–0.99]; p < 0.001). After adjustment for gestational age, invasive ventilation, postmenstrual age at discharge, WMD I°, and the type of MRI scanner statistical significance were lost for differences in FA values in the right MCP and ADC values in the left posterior limb of the internal capsule. The differences in the remaining six regions of interest were still statistically significant after adjustment for the above-mentioned variables. There were no differences in FA or ADC values in the centrum semiovale, the genu of the corpus callosum, the cerebellum, or the left occipital WM (shown in Fig. 2).

Infants Born <28 Gestational Weeks

A subgroup analysis was performed for infants born at less than 28 gestational weeks. Regarding the maternal and neonatal characteristics given in Table 1, patients in the control group more frequently showed an Apgar score below 7 at 5 min than did infants in the paracetamol group (7 [41.2%] vs. 2 [5.1%]; p < 0.001). All other variables did not differ significantly. There was no statistical difference in the incidence of brain injury.

Group comparison showed higher FA values in the paracetamol group in the left posterior limb of the internal capsule (0.63 [0.60–0.64] vs. 0.60 [0.57–0.63]; p = 0.025), in the left pons (0.34 [0.29–0.37] vs. 0.29 [0.26–0.32]; p = 0.007), in the right MCP (0.60 [0.55–0.63] vs. 0.54 [0.51–0.60]; p = 0.033), and in the splenium of the corpus callosum (0.64 [0.60–0.67] vs. 0.59 [0.46–0.64]; p = 0.016) and significantly lower ADC values in the splenium of the corpus callosum in this group (1.19 [1.09–1.25] vs. 1.28 [1.17–1.39]; p = 0.010) (shown in Fig. 3). After adjustment for the Apgar score below 7 at 5 min and the type of MRI scanner, the differences in the corpus callosum splenium and the left pons remained significant (p < 0.05).

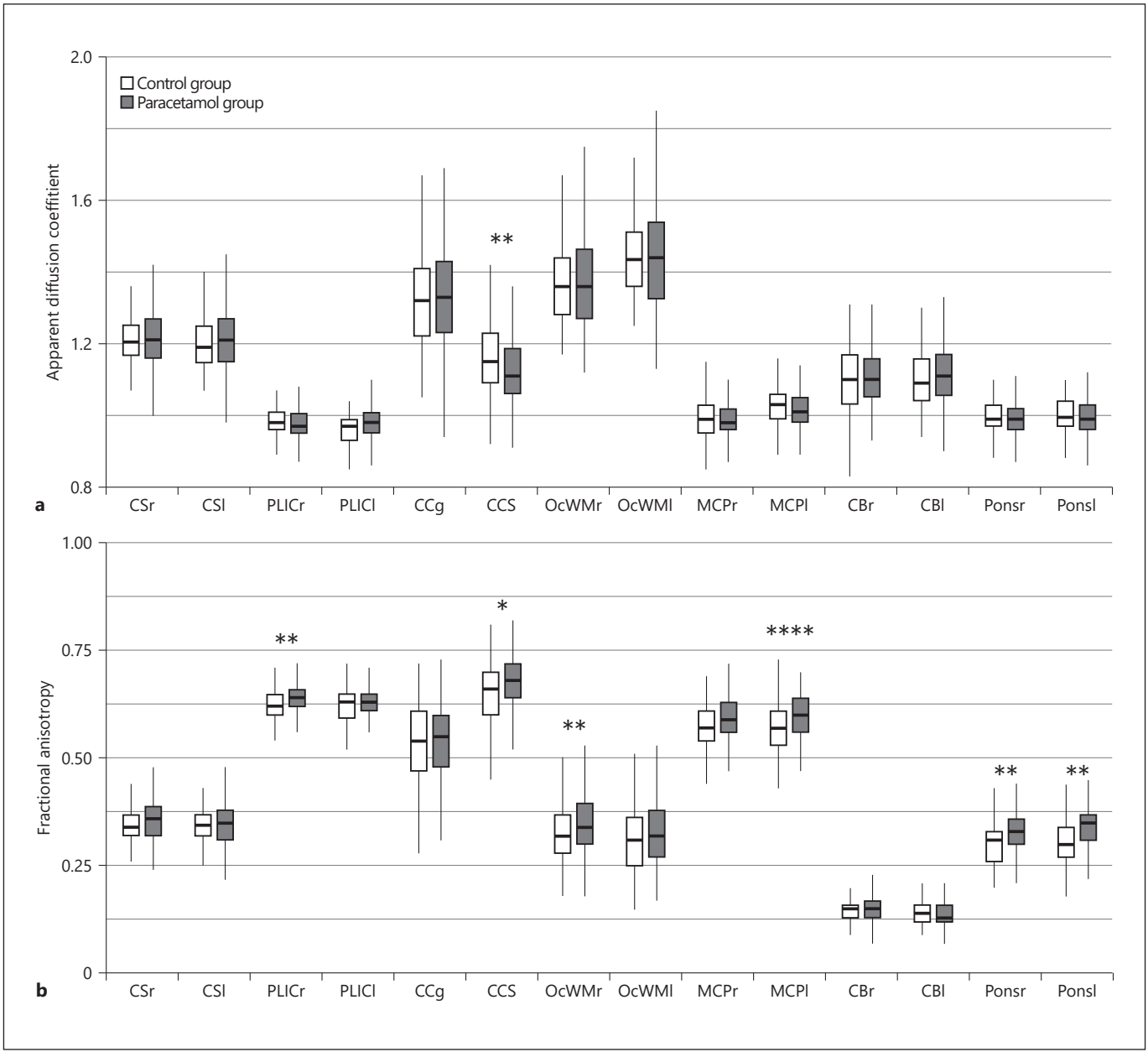

Fig. 2. a Boxplots of ADC values in the different regions of interest in the paracetamol and the control group. **b** Boxplots of FA values in the different regions of interest in the paracetamol and the control group. Significant results of the logistic regression are marked with asterisks. *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$. CS, centrum semiovale; PLIC, posterior limb of internal capsule; CCg, corpus callosum genu; CCS, corpus callosum splenium; MCP, middle cerebellar peduncle; OcWM, occipital white matter; CB, cerebellum; r, right; l, left.

Discussion

In recent years, several clinics have introduced prophylactic low-dose paracetamol administration as routine procedure in very preterm infants to induce early closure of the ductus arteriosus. To resolve the ongoing debate over the relevance of paracetamol administration in the context of prematurity, we investigated the effect of prophylactic low-dose paracetamol administration on brain development in a large cohort of very preterm infants. The infants who received prophylactic paracetamol showed more mature values in six of the regions of interest, though it was

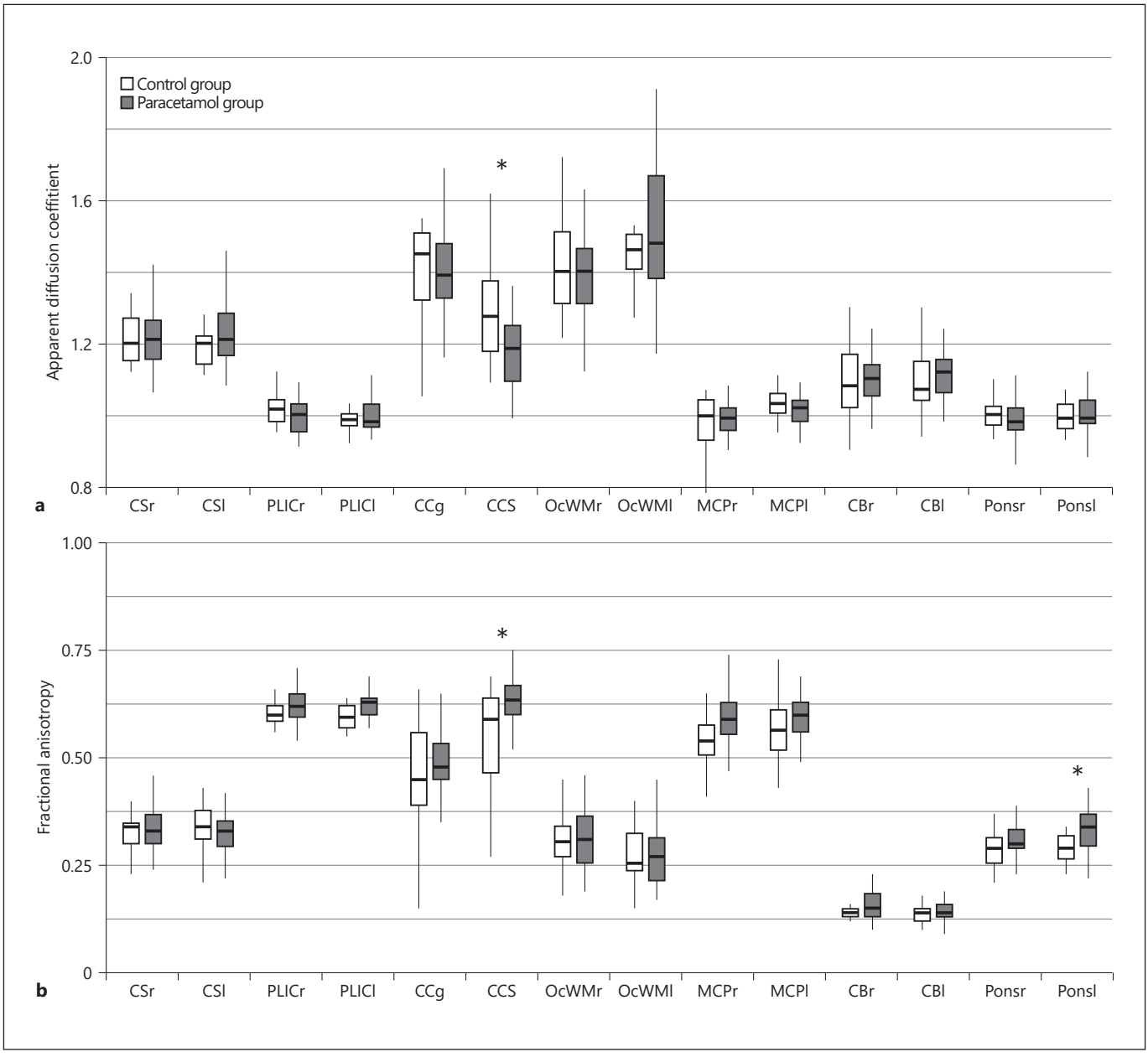

Fig. 3. a Boxplots of ADC values in the different regions of interest in the paracetamol and the control group in infants born <28 gestational weeks. **b** Boxplots of FA values in the different regions of interest in the paracetamol and the control group in infants born <28 gestational weeks. Significant results of the logistic regression are marked with asterisks. *$p < 0.05$. CS, centrum semiovale; PLIC, posterior limb of internal capsule; CCg, corpus callosum genu; CCS, corpus callosum splenium; MCP, middle cerebellar peduncle; OcWM, occipital white matter; CB, cerebellum; r, right; l, left.

the paracetamol group that included the more immature infants in terms of gestational age. Even in the group of extremely preterm infants, there was no unfavorable effect.

Paracetamol exposure during pregnancy has been linked to adverse cognitive outcomes, especially autism spectrum and attention-deficit hyperactivity disorder (ADHD) [10]. Baker et al. [21] measured paracetamol levels in meconium of 345 children and showed 2.5-fold increased odds of ADHD at the age of 6–7 years if paracetamol was detected. They found a dose-dependent

effect, with no significant risk for ADHD found at low paracetamol exposure, defined as less than the 50th percentile of all measured paracetamol levels. There was no correlation with the amount of maternal paracetamol intake. The same cohort was examined on the Wechsler Intelligence Scale for Children at the age of 6–8 years, and no statistically measurable effect was seen in relation to in utero paracetamol exposure [22]. Of course, intelligence and behavioral disorders are different neurological entities so that these results, which at first seem discordant, reflect our lack of knowledge about the effect of paracetamol on the brain. Of note, the study by Baker et al. [21] is one of the few studies that actually measured paracetamol levels and did not simply rely on questionnaires asking mothers about drug use during pregnancy. There are no data comparing the administered dose of paracetamol. There is a follow-up study of the PreParaS trial that compared intravenous paracetamol in the first 4 days of life to placebo injections (0.45% saline solution) [6]; in a very small cohort of 44 preterm infants, they found no adverse outcomes after 2 and 5 years [23, 24]. Beyond that study, the impact of postnatal paracetamol on very preterm infants has not yet been evaluated, and there are no data on potential cerebral correlates of the above-described phenomenon of paracetamol-induced neurocognitive and behavioral alterations in immature infants. We were the first to study microstructural brain development in very preterm infants with and without early paracetamol exposure. DTI offers the possibility of a quantitative characterization of the maturing WM, while conventional MRI reveals only macroscopic lesions. In general, FA increases and ADC decreases with age [25]. It has already been demonstrated that DTI measurements in preterm infants are associated with neurodevelopmental outcomes [26, 27]. Lower FA in the splenium was associated with abnormal neurodevelopment in preterm infants at 18–22 months corrected age, and higher ADC values have been shown to be an independent predictor for psychomotor delay at 2 years corrected age [28, 29]. We found higher FA values and lower ADC values in the splenium of the corpus callosum in the paracetamol group both in the overall cohort as well as in the subgroup of extremely preterm infants, indicating more mature microstructural development in this region.

We also analyzed brain injury in conventional MRI and found no differences in frequency of intraventricular or cerebellar hemorrhage but a higher incidence of WMD I° in the paracetamol group. The regression analysis showed that this finding had no statistically significant influence on our results. Furthermore, comparison of the T1-MR images during recent years (involving the paracetamol group) with T1-MR images at the beginning of the study period (involving the control group) showed a pronounced quality improvement over time, suggesting a higher detection rate of single WM hyperintensities in the paracetamol group. This is in accordance with other recent studies using high-resolution MRI that found isolated punctate WM lesions in 24% of a large cohort of very preterm infants [30].

One of the strengths of our study is the large, unselected cohort of very preterm infants. Both groups are representative of patients in a high-level neonatal intensive care unit. The retrospective study design with a historical cohort as the control group is the main limitation of this study. Since we modified birth resuscitation in recent years with the use of less-invasive surfactant administration instead of intubation, we indeed observed a lower rate of invasive ventilation in the paracetamol group. However, including invasive ventilation in our regression models did not change the results. Still, management of preterm infants is a developing process. Thus, a large, prospective randomized trial including neuroimaging to assess brain maturation and evaluation of long-term neurodevelopmental outcomes is urgently needed to provide final data on the effect of paracetamol in the immature brain of preterm infants.

Conclusion

In our study, we found no impairment of microstructural maturation processes in the brain of preterm infants at term-equivalent age following prophylactic low-dose paracetamol administration. Yet, we observed a maturational advance in some regions of interest in this group. We will further evaluate the clinical relevance of these imaging findings in the long-term follow-up. For clinicians, the results are of particular interest as this study shows reassuring neuroscientific findings on a controversially discussed but routinely used drug.

Statement of Ethics

The study was approved by the Ethics Committee of the Medical University of Innsbruck (study No. AN2013_0086 and AN2013_0086_333_4_2). As this was a retrospective analysis, written informed consent was not required.

Conflict of Interest Statement

This work was supported by Österreichischer Herzfonds. The authors have no conflicts of interests to declare.

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Author Contributions

V.N. and U.K.-K. initiated and designed the study. V.N., M.S., E.G., M.H., and M.H. participated in data collection. V.N., M.H., and T.J. evaluated the conventional MR images. Y.P., M.S., and T.J. evaluated the DTI MR images. M.S. and V.N. wrote the first draft and submitted the final version for publication. All the authors participated in data interpretation and contributed to drafting and revising the manuscript. E.R.G. and U.K.-K. supervised the study.

Data Availability Statement

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

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