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Follow-up study of the early, randomised paracetamol trial to preterm infants, found no adverse reactions at the two-years corrected age

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Short title: Early paracetamol trial's follow-up study

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ABSTRACT

Aim: We examined the long-term outcomes and safety of early intravenous paracetamol for ductus arteriosus closure at a corrected age of two years.

Methods: This was a follow-up of the 2013-2014 randomised, double-blind Preterm Infant's Paracetamol Study at Oulu University Hospital, Finland, which recruited 48 very preterm infants within 24 hours of birth. They received intravenous paracetamol or a placebo for four days. In 2015-2017 we followed up 44 infants (92%) at two years of corrected age. This included clinical and neurodevelopmental assessments and a parental medical history questionnaire.

Results: The 44 infants (55% boys) were born at 23^{5}-31^{6} weeks of gestation. No differences in the cardiac parameters, including blood pressures and ultrasound scan results, were found. Neurodevelopmental stages, as quantified by the Griffiths test, were similar. No signs of autism were reported. Asthma medication was more common in the control group, but the difference was not significant. Atopy scores, numbers of infections, and the use of public health services were similar between the two groups.

Conclusion: No long-term adverse reactions of early intravenous paracetamol were detected two years later. Larger trials are needed on the safety and efficacy of paracetamol prophylaxis for early ductal closure in very preterm infants.

Keywords: acetaminophen; asthma; neurodevelopment; patent ductus arteriosus; premature infant

KEY NOTES

- Early intravenous paracetamol for very preterm infants is well tolerated but there is no data on long-term consequences.
- Children enrolled in a randomised trial, were studied at two years of age by cardiac and neurodevelopmental examinations, and by parental questionnaire.
- Although no differences between paracetamol and placebo groups were found, more evidence is needed to establish safety and potential benefits.

INTRODUCTION

In preterm infants, patent ductus arteriosus (PDA) may increase the risks of serious complications related to prematurity. These complications may include bronchopulmonary dysplasia, intraventricular haemorrhage, necrotising enterocolitis, pulmonary haemorrhage, and retinopathy of prematurity (1,2). PDA therapies such as ibuprofen, indomethacin or surgical ligation may have serious adverse effects (2-4). Previous studies have suggested that paracetamol (acetaminophen) may be used as an alternative medication, decreasing the need for PDA therapies in very low post menstrual age (PMA) infants, born before 32 weeks of gestation (5-10). The neurodevelopmental outcomes of administering paracetamol to preterm infants have been examined in a previous follow-up study conducted 18 to 24 months after birth, but otherwise the long-term adverse reactions are still unknown (11).

Paracetamol is one of the most commonly used analgesic and antipyretic drugs. It is the drug of choice for patients who cannot use non-steroidal anti-inflammatory drugs, such as pregnant or breastfeeding women (12). A number of cohort studies on maternal paracetamol use during pregnancy have recently been published (13). In these studies, paracetamol was not teratogenic, but

it has been variably associated with different adverse outcomes in the offspring, including neurological and respiratory problems (14-17). However, there is a lack of controlled, prospective, long-term outcome studies about the early use in preterm infants (18).

We previously conducted a phase II, randomised, controlled, double-blind clinical trial of paracetamol prophylaxis for ductal closure in very low PMA infants, the Preterm Infants' Paracetamol Study (PreParaS) (7). In the present follow-up study, we studied the paracetamol and placebo group infants at a corrected age of two years. The current study included cardiac and neurodevelopmental examinations and a parental questionnaire addressing morbidities, hospitalisations, medications, infections, and atopic and other symptoms. Our aim was to evaluate the long-term safety of early intravenous paracetamol for very low PMA infants. We hypothesised that no serious outcomes would emerge in the patients treated with paracetamol.

PATIENTS AND METHODS

The participants in the present follow-up study were enrolled in the PreParaS trial from September 2013 to December 2014, which was conducted in the neonatal intensive care unit of Oulu University Hospital, Oulu, Finland, as previously described in detail (7). Before one-day of age, these very preterm infants, born at 23^{5} to 31^{6} weeks of gestational age, of whom 56 % were boys, were randomly selected to receive either a placebo or intravenous paracetamol for four days (Table S1). In present follow-up study, the patients were examined approximately two years after the expected due date. From PreParaS trial, 44/48 patients were included in the follow-up study between December 2015 and March 2017 (Figure 1). The exclusion criteria were chromosomal or another abnormalities causing a neurodevelopmental disability and a native language other than Finnish because neurological tests were conducted in Finnish.

The original trial and the follow-up research plans were approved by the regional ethics board. The original trial registration can be found on ClinicalTrials.gov (NCT 01938261) and in the European Clinical Trials Database (EudraCT 2013-008142-33). This follow-up study was included in these trial applications. The parents of all the participating children provided written informed consent.

The primary outcome of this study was the occurrence of the long-term adverse reactions in the participants of the PreParaS trial. The secondary outcomes included all the parameters of the cardiac and neurodevelopmental examinations and of the parental questionnaire.

A resident (PP) specialising in paediatrics and subspecialising in paediatric cardiology performed the blind cardiac ultrasound examinations except those of two patients (twins), who were examined in their hometown hospital by the local paediatric cardiologist (19). Z-scores were calculated for the left ventricular measurements and tricuspid annular plane systolic excursion (TAPSE) (20,21). Systolic and diastolic blood pressures (mmHg) were measured on the right arm and right leg.

A paediatrician specialising in paediatric neurology (HK) performed the blind neurodevelopmental testing using the Griffiths Mental Development Scales (GDMS), Extended Revised: two to eight years (22). The GDMS includes five subscales: locomotor, personal-social, hearing and language, hand and eye coordination, and performance. These were tested, scored, and rated individually for each participant. All the raw scores were converted to standard scores (general quotient, Z-scores) according to the corrected age using the tables in the Griffiths test analysis manual.

The self-administered questionnaire was sent to the children's homes or (parents or guardians of the child) before the follow-up visits. It included questions about the child's health and development during the two years after the first discharge from the hospital. The questions addressed cardiac, respiratory, and atopic symptoms; neurological development; infections; hospital treatments since the initial discharge; and medications. Atopic symptoms and therapies were recorded, and each patient's atopic tendency was defined using a calculated atopy scoring system. This system included six dichotomous variables, each of which added one point to the score when positive: any respiratory symptoms, hospitalisation due to respiratory symptoms, the need for asthma medication, any skin symptoms, hospitalisation due to skin symptoms, and a diagnosed allergy. Three continuous variables were also included and points were added accordingly: the number of different respiratory symptoms, the number of asthma medications, and the number of skin creams or other dermatological medications needed. Each child's weight, length, and head circumference at the age of two years were also recorded.

The statistical analyses were performed using IBM SPSS Statistics, Version 23 (IBM Corporation, New York, USA). The variables were analysed using an independent-samples t-test, a Pearson's chi-square test, or an independent-samples Mann-Whitney U test, as appropriate. The limit of significance was $p<0.05$.

RESULTS

In this follow-up study, forty-four children (92% of the original group) participated (Figure 1) at the corrected age of two years. Four infants did not participate for various reasons. One infant in the placebo group had died one month after birth. Parents of two children denied consent for the follow-up study. One study patient was excluded after diagnosis of a chromosomal defect predisposing the child to neurodevelopmental delay. Two other children (twins) were not invited to participate in the

GDMS testing because they didn`t speak Finnish as a native language. The parents of all 44 participating children filled out the questionnaire. Of these, 23 were in the original paracetamol group and 21 were in the placebo group. Cardiac examinations were performed on 36 children, and 35 participated in the neurodevelopmental testing. A total of 31 patients participated in all parts of the follow-up study, 18 from the paracetamol group and 13 controls.

The cardiac ultrasound results were similar in both groups (Table 1). No open ductus was detected in any child. There wasn`t any difference in systolic blood pressures, p=0.275, or in diastolic blood pressures, p=0.712, between the groups. The left ventricular measurements and their calculated Z-scores did not differ either. The TAPSE values of the study children and their calculated Z-scores exceeded the previously set normal values for the age group but did not differ between the two study groups (20,21). These values were correlated to present and previous morbidities to explore the possible connection to infancy. The only significant correlations were the age of ductal closure (TAPSE, r=-0.52, p=0.003; Z-score, r=-0.51, p=0.004) and PDA diagnosis (TAPSE, r=-0.51, p=0.003; Z-score, r=-0.50, p=0.004). Furthermore, there were tendencies to correlate to all the given PDA therapies: the need for ibuprofen medication (TAPSE, r=-0.34, p=0.065; Z-score, r=-0.33, p=0.072), the number of ibuprofen doses (TAPSE, r=-0.34, p=0.063; Z-score, r=-0.34, p=0.071), and the need for ligation (TAPSE, r=-0.34, p=0.065; Z-score, r=-0.33, p=0.072).

The participants' neurodevelopmental stages were quantified using the GDMS test (Table 2). No significant differences between the two groups were found. In the paracetamol group, the mean standard deviation (SD) personal-social skills score was 26.5 (3.2); it was 26.7 (3.1) in the control group, p=0.843. Mean (SD) language scores were 23.8 (5.1) and 22.9 (4.9), p=0.608, respectively. The total raw mean score (SD) from all five sub-scales was 24.0 (2.4) for the paracetamol group and 23.5 (2.2) for the placebo group, p=0.478. In the parental questionnaires, some neurodevelopmental

abnormalities were reported in four cases (Table 2). Two children, one in the paracetamol group and one in the placebo group, had developmental dysphasia. One child in the paracetamol group presented mild cerebral palsy. One child in the placebo group had severe neurological sequelae, including epilepsy, hydrocephalus, mental retardation, and severe cerebral palsy. Six (26%) children in the paracetamol group and five (24%) in the placebo group had speech, occupational, or physiotherapy some time during the two-year follow-up period, p=0.862. No child was reported to have autistic behaviour at the age of two.

The responses to the parental questionnaire did not indicate any differences in growth, atopic tendencies, infections, or the use of public health services between the two groups (Table 3). Asthma medication was slightly less common in the paracetamol group than in the placebo group, n=3 (13 %) vs. n=6 (29 %), p=0.202. The atopy scores mean (SD) was 3.1 (3.9) in the paracetamol group and 2.3 (2.9) in the control, p=0.439. The reported occurrences of infections and antibiotic treatments were similar in both groups.

DISCUSSION

In the present two-year follow-up study of a placebo-controlled trial for enhancing ductal contraction shortly after birth, early intravenous paracetamol was found to be safe, without any detectable long-term adverse reactions. The paracetamol dosages were determined based on the manufacturer's recommendation for the treatment of pain. Larger trials and a longer period of follow up are, however, needed to ensure the safety of this medication and the absence of serious long-term adverse reactions.

The growth and development of very low PMA infants who received paracetamol were prospectively monitored and blindly compared to those of the very low PMA infants who received placebos. As expected with the moderate dosing schedule, no differences between the two groups emerged in any of the study fields observed in this rather limited study. Since the outcomes of intravenous paracetamol have some haemodynamic consequences, we wanted to conduct a comprehensive cardiac examination in order to ascertain the safety of intravenous paracetamol in infants. No cardiovascular adverse reactions were detected (Table 1). The significant negative correlations of the high TAPSE values and their Z-scores to the ductal closure age and PDA diagnosis have not been reported earlier. This may be a coincidence, or possibly reflect the long-term advantage of the early ductal closure to the cardiac function of a preterm infant. Furthermore, according to the results of this study, the participants' early neurodevelopment was not compromised by the early use of paracetamol. The few reported neurological diagnoses and the occasional need for therapies in study participants are typical for preterm infants and did not differ between the two groups (Table 2). This is in line with the previous study of very preterm infants born before 30 gestation weeks, PDA treated with oral paracetamol or ibuprofen, and studied at the developmental age of 18 to 24 months (11). No differences in the Bayley scales of the two groups were found. Apart from these two studies, no controlled long-term data after early paracetamol use for very low PMA infants has been reported.

Paracetamol is known to cross the placenta barrier, suggesting that the developing foetus could experience side effects. Some cohort studies on maternal paracetamol use during pregnancy and the possible long-term adverse reactions on the foetus have been published. In some of them, maternal paracetamol use was associated with childhood autism spectrum disorders and a higher risk of behavioural problems (14,15,23). A number of cohort studies have also found an association between asthma and paracetamol exposure during pregnancy or early childhood (16). In general, observational studies are subject to several biases and offer weak evidence for causation. More than half of

pregnant women in the USA and Europe report using paracetamol and it is the most common drug administered to children; as a result, it is difficult to connect these exposures to specific diagnoses (24). In animal models, the impact of prenatal paracetamol exposure to offspring has been somewhat varied. After paracetamol was administered to pregnant mice, the adult offspring demonstrated airway inflammation and severe neurodevelopmental aberrations (25,26). Meanwhile, other studies have found the opposite, concluding that paracetamol use during pregnancy does not cause increased neurodevelopmental symptoms or allergic airway diseases in the offspring (27,28). The present study found no differences in the participants' neurodevelopment, nor any symptoms that would indicate the development of autism spectrum diseases or asthma, although it is known that autism spectrum disorders are seldom diagnosed before the age of three years (Table 2 and 3).

This study has some limitations. As in the original trial, the sample size was small. Therefore, the results are prone to beta errors, and the possibilities of minor differences will be unsettled until larger trial results are available. However, no major problems or defects were found to correlate with early paracetamol administration in this study. This study was conducted at a corrected age of two years, which created some challenges for the cardiac and neurological examinations, as they depended on the children's voluntary cooperation. Age-related behaviours explain why not all examinations were conducted on every participant. However, no differences were found between the outcomes of the two groups. The neurological examination used the Griffiths Mental Development Scales, Extended Revised, which covers children aged two to eight. The study equipment was designed for children over two years of age, and the tests' scoring scales start at the age of two years. It became obvious that some of the study participants had not yet reached the developmental age of two years. This may explain why our study population had constantly lower Z-scores than the original reference population (Table 2). Additionally, both our study groups consisted of very low PMA infants who required intensive care for quite a long period and may still demonstrate developmental delays at the corrected age of two years.

CONCLUSION

We conducted the first placebo-controlled follow-up study of the cardiac, neurodevelopmental, and other possible long-term adverse reactions of early intravenous paracetamol. The two-year outcomes of these very preterm children did not differ between the paracetamol group and the placebo group. Paracetamol prophylaxis is possibly safe and effective for enhancing the closure of the patent ductus arteriosus in very preterm infants. It may also decrease the need for morphine during respiratory treatment (29,30). These results suggest that the benefits of the early use of intravenous paracetamol outweighed the long-term risks. However, larger trials are needed to ensure the long-term safety of intravenous paracetamol in preterm infants.

ABBREVIATIONS

GDMS	Griffiths Mental Development Scales
PDA	Patent ductus arteriosus
PMA	Post menstrual age
PreParaS	The Preterm infants' Paracetamol Study
SD	Standard deviation
TAPSE	Tricuspid annular plane systolic excursion

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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FIGURE LEGEND

Figure 1. Flowchart of the patients.

Table 1 Blood pressure and cardiac ultrasound examination results

	Paracetamol group n = 18		Placebo group n = 18		p value
		Z-score		Z-score	
Blood pressure (right arm): systole, mmHg	104.8 (8.8)*	.	98.5 (14.8)†	.	0.275
diastole, mmHg	62.6 (8.0)*	.	61.4 (6.0)†	.	0.712
Open ductus, n (%)	0	.	0	.	N/A
Left atrium to aorta ratio	1.33 (0.13)	.	1.28 (0.14)	.	0.330
Tricuspid regurgitation, m/s, median (range)	0 (0-2.5)	.	0 (0-2.1)	.	0.389‡
Tricuspid annular plane systolic excursion, mm	19.6 (2.1)§	2.7 (1.4)¶	19.2 (5.8)**	3.1 (2.2)**	0.801
Left ventricle: septum, mm	5.3 (0.9)	0.5 (0.9)	5.2 (0.9)	0.5 (0.8)	0.681
posterior wall, mm	4.9 (1.1)	0.9 (1.3)	4.8 (0.7)	0.9 (0.8)	0.727
end-systolic diameter, mm	18.7 (1.5)	0.1 (0.5)	17.8 (2.0)	-0.1 (0.7)	0.163
end-diastolic diameter, mm	29.0 (2.7)	-0.4 (0.7)	27.9 (3.4)	-0.5 (1.1)	0.313
Fractional shortening, %	35.6 (2.0)	.	35.9 (2.4)	.	0.677
Ejection fraction$_{Teich}$, %	66.7 (2.3)	.	67.0 (3.1)	.	0.717

Independent-samples t-test was used, except ‡Mann Whitney U test. All values are mean (SD) unless otherwise stated.

*n=9, †n=12, §n=15, ¶n=14, ** n=17.

Table 2 Neurodevelopmental outcomes using the Griffiths Mental Development Scales test and neurological diagnoses according to the parents' responses

Griffiths Mental Development Scales test*	Paracetamol group n=19	Placebo group n=16	p value
Total Raw Scores: All sub-scales	24.0 (2.4)	23.5 (2.2)	0.478
Z-scores	-1.4 (0.7)	-1.5 (0.7)	0.475
Sub-scales: Locomotor	17.5 (8.3)	14.0 (10.1)	0.199
Personal-social	26.5 (3.2)	26.7 (3.1)	0.843
Hearing and language	23.8 (5.1)	22.9 (4.9)	0.608
Hand and eye coordination	23.0 (2.0)	22.5 (2.7)	0.521
Performance	25.5 (4.7)	23.9 (4.2)	0.304
Parental questionnaire†	n=23	n=21	
Developmental dysphasia	1 (4.3)	1 (4.8)	0.947
Autistic behaviour	0	0	N/A
Muscular dystonia	1 (4.3)	0	0.334
Mild cerebral palsy	1 (4.3)	0	0.334
Severe cerebral palsy	0	1 (4.8)‡	0.290
Need for speech, occupational, or physiotherapy	6 (26.0)	5 (23.8)	0.862
Epilepsy or convulsions	0	1 (4.8)‡	0.290
Severe neurological sequelae	0	1 (4.8)‡	0.290

*Independent-samples t-test was used. All values are expressed as mean (SD).

†Pearson's chi-squared test was used. All values are expressed as n (%).

‡These entries represent the same individual.

Table 3 Growth, infections, atopic tendencies, and physician contacts, according to the parental questionnaire

	Paracetamol group n=23	Placebo group n=21	p value
Weight, kg, mean (SD)	11.7 (1.3)*	11.1 (1.6)	0.129†
Length, cm, mean (SD)	85.4 (3.2)*	85.1 (4.2)	0.792†
Head circumference, cm, mean (SD)	48.7 (1.3)*	48.7 (1.7)	0.986†
Child welfare control policlinic extra visits due to slow growth, n (%)	0	2 (9.5)	0.130§
Infections, n, median (range)	5.0 (0-20)	4.0 (1-10)	0.256‡
Periods of antibiotics, median (range)	2.0 (0-12)	2.0 (0-7)	0.886‡
Any allergy diagnosis, n (%)	1 (4.3)	2 (9.5)	0.496§
Asthma medication, n (%)	3 (13.0)	6 (28.6)	0.202§
Atopy scores, mean (SD)	3.1 (3.9)	2.3 (2.9)	0.439†
General practitioner visits and hospitalizations for any reasons, n, median (range)	0.5 (0-5)	0.5 (0-4)	0.938§

*n=22.

†Independent-samples t-test; ‡Independent-samples Mann-Whitney U test; §Pearson's chi-squared test.