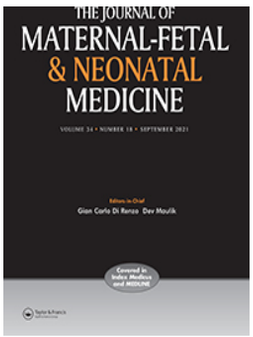

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SHORT REPORT

Trial of paracetamol for premature newborns: five-year follow-up

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ABSTRACT

Introduction: Paracetamol is a commonly used pain medication for the very-high risk neonates and it is increasingly being used for patent ductus arteriosus treatment in preterm infants. However, randomized trial data on long-term consequences are not yet available, but there is some evidence of serious adverse effects on children exposed to paracetamol during pregnancy.
Patients and methods: A five-year follow-up study of a placebo-controlled paracetamol trial on very preterm infants (PreParaS) was conducted ($n = 48$). Using a web-based parental questionnaire, parents answered questions about their children's cardiac and respiratory symptoms, allergies, neurodevelopment, infections, medications and hospitalizations.
Results: Most parents reported that their child had normal development (paracetamol 79% vs. placebo 65%). Physician-diagnosed asthma or allergy (paracetamol 10.5% vs. placebo 25.0%), or hospitalization due to respiratory symptoms (0 vs. 15%) were uncommon and neurological or neuro-psychiatric symptoms were rare.
Conclusions: Current follow-up results on paracetamol-exposed very preterm infants may not be alarming suggesting that paracetamol administration shortly after birth is not associated with common adverse consequences.

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Acetaminophen; child development; long-term adverse effects; outcome assessment; questionnaire

Introduction

Paracetamol (acetaminophen) has been one option for neonatal pain therapy, and recently, it has been suggested as a novel treatment for patent ductus arteriosus of the preterm infants [1, 2]. As randomized trials and cohort studies have found it well tolerated even among the most premature infants, the question about long-term safety has emerged [3]. Neonates, and especially preterm infants, could be vulnerable to medical adverse effects that may be diagnosed later.

Long-term follow-up data from randomized placebo-controlled trials on neonatal paracetamol treatment are not available. In contrast, numerous epidemiological studies about maternal paracetamol use during pregnancy and its potential associations with worrisome long-term effects on the offspring have been published [3]. Some small follow-up studies, two years after the randomization of preterm infants to paracetamol, reported that no serious long-term outcomes were associated with early paracetamol [4, 5]. In addition, an epidemiological study did not associate neonatal paracetamol administration during intensive care soon after birth to any previously suggested long-term morbidities, either [6].

To study the possible long-term adverse effects of an early paracetamol treatment trial, we conducted a web-based parental survey for these patients at five years of age. The focus was symptoms and diseases, such as allergic and developmental disorders, that are suggested consequences of early paracetamol exposure.

Materials and methods

The present study is the follow-up of the Premature infants' Paracetamol Study (PreParaS, NCT01938261, EudraCT 2013-008142-33) at the age of five years [1]. The participants were very preterm infants (gestation 23^5–31^6 weeks) born between 18.9.2013 and 29.10.2014 in Oulu University Hospital, Oulu, Finland. In the PreParaS trial, very preterm infants ($n = 48$) were randomly assigned to paracetamol or placebo. After a loading dose (20 mg/kg), paracetamol-group infants received 7.5 mg/kg intravenous paracetamol every six hours for four days. Accordingly, placebo group had 0.45% saline solution. The exclusion criteria for the follow-up study

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were major malformations and chromosomal defects with neurodevelopmental challenges.

An internet-based, self-administered questionnaire was emailed to parents, and the results were compiled using Webropol 3.0 (Webropol Oy, Helsinki, Finland). The questions concerned the child's health and development during the five years after the first discharge from the hospital, and addressed cardiac, respiratory, atopic, and allergy symptoms, neurological development, required medications, infections and hospital treatments since the initial discharge.

The statistical analyses were performed using IBM SPSS Statistics, version 25 (IBM Corporation, New York, NY, USA). The variables were analyzed using Pearson's chi-squared test. The limit of significance was $p < .05$.

Ethics

The Ethical board of the Northern Ostrobothnia hospital district approved the original trial and follow-up research plans.

Results

Altogether 39 infants were studied, 19 in the paracetamol group and 20 in the placebo group, comprising 81% of the original sample size (Figure 1). Of the excluded infants, one had died at the age of one month, one had been diagnosed with a chromosomal abnormality likely to affect the neurodevelopment, and seven infants' parents refused to participate in this five-year follow-up study. There were no significant differences in atopy or allergies, in asthma diagnoses and the need for asthma medication between the two groups (Table 1). Most parents reported that their child had developed normally without long-term diseases (paracetamol group, $n = 15$ [78.9%] vs. placebo $n = 13$ [65.0%], $p = .480$, Table 1). The numbers of the inquired long-term diagnoses needing medications and treatments were similar in both groups (Table 1).

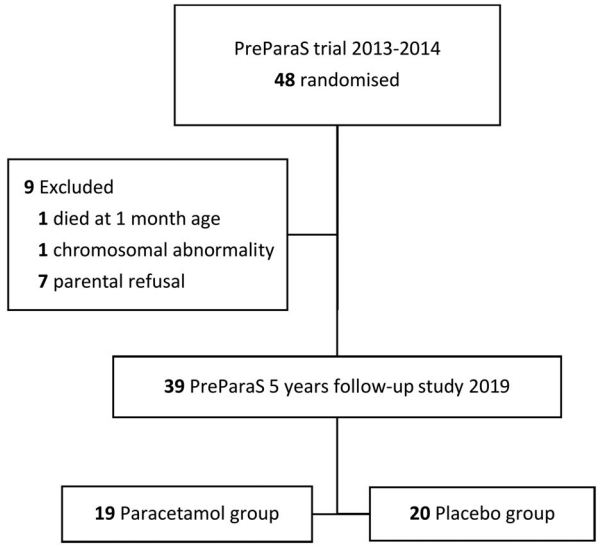

Figure 1. Flow chart of the study patients. PreParaS, Premature infants' Paracetamol Study.

Discussion

At the five-years of age, no increase in the numbers of common childhood diseases were found in the participants of present early placebo-controlled paracetamol trial. Based on the current study, we report that paracetamol administration to very premature infants may not be associated with asthma or allergies.

The follow-up data on early paracetamol exposure is mostly from epidemiological studies that reviewed maternal paracetamol use during pregnancy, suggesting that, besides asthma and allergies, paracetamol causes other severe childhood diseases, including cerebral palsy, and neuro-psychiatric disorders. However, in these studies, the recall bias has mostly not been ruled out, and conflicting results have been published. Our results, which are in line with paracetamol trials' two-year follow-up results and the epidemiological five-year follow-up study, reveal no differences in the neurological childhood diseases after neonatal intravenous paracetamol exposure [4–6].

Present pilot study of a randomized trial has limitations. This study has a small sample size, thereby significantly affecting our ability to draw concrete conclusion. In addition, as the study was designed as a self-administered web-based questionnaire survey, there is an inherent component of self-response bias; hence, the results should be interpreted very cautiously. Although no increase in common respiratory symptoms was evident after neonatal paracetamol exposure, the sample size is still not sufficient for detecting rare adverse effects in neurological development [6]. The parents reported normal neurodevelopment in 72% of the children in the present five-year follow-up (Table 1). In our previously published register-based five-year study, the diagnosed neurological abnormality rate in children after neonatal intensive care (22% very preterm births <32 gestation wk) was only 8.1% [6]. In contrast, in a subset of the Boston birth cohort, the concentration of paracetamol or its metabolites in the cord blood associated with neurodevelopmental risk [7]. In that study, at a mean age of 9.8 years of follow-up, only 33% had normal neurodevelopment in an external evaluation of a population consisting of 18% preterm births. In the follow-up studies on children exposed to paracetamol as newborn infants, no increase in morbidities was evident [8, 9]. This raises the possibility that toxic paracetamol

Table 1. Outcomes of the randomized infants at the five years of age, *n* (%); Pearson's chi-squared test.

	Paracetamol group $n = 19$	Placebo group $n = 20$	*p* Value
Atopy	3 (15.8)	2 (10.0)	.661
Any allergy, diagnosed by a physician	0	3 (15.0)	.231
Asthma, diagnosed by a physician	2 (10.5)	5 (25.0)	.407
Asthma medication	5 (26.3)	4 (20.0)	.716
Medical visits due to respiratory symptoms	6 (31.6)	9 (45.0)	.522
Hospitalization due to respiratory symptoms	0	3 (15.0)	.229
Normal development	15 (78.9)	13 (65.0)	.480
Need for speech, occupational, or physiotherapy	10 (52.6)	12 (60.0)	.751
Autism spectrum disorder	0	0	NA
Attention deficit hyperactivity disorder	0	1 (5.0)	1.000
Cerebral palsy	1 (5.3)	1 (5.0)	1.000
Intellectual disability	1 (5.3)	2 (10.0)	1.000
Pervasive developmental disorder	0	1 (5.0)	1.000
Developmental delay of speech and language	2 (10.5)	3 (15.0)	1.000
Epilepsy	0	1 (5.0)	1.000
Inflammatory bowel diseases	0	0	NA
Rheumatoid arthritis	1 (5.3)	1 (5.0)	1.000

NA: not applicable.

metabolites from the mother may be dose-dependently harmful to the fetus while neonatal administration may be better tolerated, possibly due to the immaturity of the hepatic enzymes that catalyze formation of toxic N-acetyl-p-benzoquinone imine metabolites [10]. Further follow-up studies with a robust standardized testing for neurodevelopmental outcomes are required to assess the safety of paracetamol as it is already being used in neonatal units. As opposed to biases of epidemiological surveys, the present data, although clearly insufficient in size, are from a randomized, double-blind study.

To conclude, paracetamol use for premature newborn infants did not increase long-term respiratory morbidities in our patient population. Large randomized trial with standardized follow-up protocol should be conducted to detect any potential association with early neonatal paracetamol treatment and adverse neurological outcomes, like autism spectrum disorders and attention deficit hyperactive disorder.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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