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Analgesic dose of paracetamol and artificial ventilation – effects on ductus arteriosus patency in very and extremely preterm infants

Przeciwbólowa dawka paracetamolu i sztuczna wentylacja – wpływ na drożność przewodu tętniczego u skrajnych i bardzo skrajnych wcześniaków

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Abstract

Introduction and objective: Patent ductus arteriosus is a heart defect primarily associated with extreme prematurity. It can lead to multiple morbidities due to diminished organ perfusion or a left-to-right shunt. It can be treated with paracetamol, among other options. Treatment includes fluid restriction, pharmacotherapy (paracetamol at a dose of 15 mg/kg, non-steroidal anti-inflammatory drugs), percutaneous interventions, and surgical ligation. This retrospective study aims to analyse whether the analgesic dose of paracetamol and artificial ventilation has any effect on the occurrence of ductus arteriosus. **Materials and methods:** Ninety-four prematurely born neonates (<32 weeks of gestation) between 2020 and 2023 were included in the study. The dose of paracetamol, surfactant supply, and steroid therapy in the prenatal period were analysed up to the first echocardiographic examination. Additionally, data were collected about the type of ventilation during the examination. Logistic regression was used to evaluate predictive factors for PDA presence. **Results:** The median gestational age and weight were 30 weeks and 1290 g, respectively. Among 49 preterm neonates treated with intravenous paracetamol at an analgesic dose of ≤10 mg/kg, the risk of ductus arteriosus patency was lower ($p = 0.002$). Both non-invasive and mechanical ventilation increased the risk of ductus patency ($p = 0.042$, $p = 0.044$). There was no significant relationship between previous ductus and surfactant treatment or prenatal steroid use ($p = 0.611$, $p = 0.93$). **Conclusions:** Paracetamol in an analgesic dose reduces the likelihood of open ductus arteriosus in extremely and very premature infants. Additionally, artificial ventilation is a significant factor affecting ductus patency.

Keywords: patent ductus arteriosus, paracetamol, non-invasive ventilation, mechanical ventilation, preterm infants

Streszczenie

Wprowadzenie i cel: Przetrwały przewód tętniczy jest wadą serca, najczęściej związaną ze skrajnym wcześniactwem. Może prowadzić do przeciążenia objętościowego serca, łożyska płucnego i hipoperfuzji narządowej w wyniku podkradania krwi z krążenia systemowego. Otwarty przewód można leczyć m.in. restrykcją płynową, farmakoterapią (niesteroidowymi lekami przeciwzapalnymi lub paracetamolem w dawce 15 mg/kg), przezskórnym zabiegiem interwencyjnym oraz chirurgicznym podwiązaniem przewodu. Celem badania była ocena, czy paracetamol w dawce przeciwbólowej (≤10 mg/kg) i sztuczna wentylacja mają jakikolwiek wpływ na częstość występowania otwartego przewodu tętniczego. **Materiał i metody:** Do badania włączono 94 noworodki urodzone <32. tygodnia ciąży między 2020 a 2023 rokiem. Analizowano wielkość dawki paracetamolu, podaż surfaktantu, prenatalne stosowanie steroidów do momentu wykonania pierwszego badania echokardiograficznego i dane dotyczące rodzaju wentylacji pacjenta podczas badania. Do oceny czynników predykcyjnych obecności przewodu tętniczego użyto regresji logistycznej. **Wyniki:** Mediana wieku ciążowego i masy ciała wynosiła

odpowiednio 30 tygodni i 1290 gramów. 49 noworodków otrzymywało leczenie paracetamolem dożylnie w dawce przeciwbólowej ≤10 mg/kg, co było związane z mniejszym ryzykiem drożności przetrwałego przewodu tętniczego (p = 0,002). Dodatkowo przepływ przez przewód tętniczy był częstszy u pacjentów poddanych wentylacji nieinwazyjnej i mechanicznej (p = 0,042, p = 0,044). Nie stwierdzono istotnego związku między otwartym przewodem tętniczym a leczeniem surfaktantem i prenatalnym stosowaniem steroidów (p = 0,611, p = 0,93). **Wnioski:** Paracetamol w dawce przeciwbólowej zmniejsza prawdopodobieństwo otwartego przewodu tętniczego w grupie skrajnych i bardzo skrajnych wcześniaków. Co więcej, sztuczna wentylacja jest dodatkowym czynnikiem ryzyka otwartego przewodu.

Słowa kluczowe: przewód tętniczy, paracetamol, wentylacja nieinwazyjna, wentylacja mechaniczna, wcześniaki

INTRODUCTION

The ductus arteriosus (DA) is a connection between the main pulmonary artery and the aorta. Typically, its functional closure occurs within the first 72 hours of life[1]. When it fails to close within this period, it is termed a patent ductus arteriosus (PDA), and its prevalence is inversely proportional to gestational age (GA) and body weight[2,3].

In preterm infants, the DA may remain open for an extended period, mainly due to a higher oxygen response threshold. Also, the smooth muscle of the ductus is hypersensitive to the vasodilatory effects of nitric oxide (NO) and prostaglandins (PG). Furthermore, the muscle has a diminished ability to contract properly due to its immaturity[1,4].

There is ongoing debate about whether PDA should be treated, with some arguing that its presence is physiological and that a watch-and-wait approach may lead to its spontaneous closure without unnecessary medical intervention or complications[5,6]. However, with conservative treatment, spontaneous closure usually takes longer, thereby prolonging the duration of the left-to-right shunt[2,3].

Moreover, PDA can be associated with various morbidities, either due to the steal phenomenon or the direct increase in pulmonary blood flow and heart volume overload. This, in turn, can result in pulmonary oedema, and haemorrhage, and also can predispose to bronchopulmonary dysplasia (BPD) or necrotising enterocolitis (NEC)[7].

That is why medical intervention for PDA closure, especially in extremely premature infants, can be more beneficial than some believe, despite the potential side effects associated with treatment[8,9].

When it comes to pharmacological treatment, it seems that the administration of either paracetamol, ibuprofen, or indomethacin is equally effective for PDA closure[10]. When medications fail, PDA can be closed by ligation; however, this procedure carries a higher risk of adverse side effects[11].

Paracetamol is associated with fewer complications than ibuprofen or indomethacin, particularly in terms of gastrointestinal bleeding, renal function, or platelet count. However, it can still affect the liver, causing a transient increase in enzyme levels. Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or indomethacin, cause vasoconstriction, whereas paracetamol has a vasodilatory effect, which may explain the lack of serious side effects that are observed with its use[10]. Additionally, paracetamol is more effective in promoting ductus arteriosus closure when administered early after birth[12].

When PDA leads to organ hypoperfusion or its flow has a growing pattern in pulsed Doppler, it is classified as a hemodynamically significant PDA (hsPDA) and is treated with paracetamol at a dose of 15 mg/kg administrated every 6 hours, from 5 to 7 days[10,13]. However, the analgesic protocols typically involve doses between 7.5 and 10 mg/kg, administered from 3 to, rarely, 4 times daily, sometimes with a loading dose of 20 mg/kg[14]. The duration of use depends on the signs of pain presented by a newborn.

The principal aim of this study was to examine whether a reduced dosage of paracetamol used in analgesia from the first days of life has any impact on ductus arteriosus patency. Additionally, the study sought to identify other variables that might be associated with ductal patency.

MATERIALS

In this retrospective, single-centre study, a total of 94 infants were included. Patients were admitted to the Neonatal Intensive Care Unit at the Level III Children's Hospital, Medical University of Warsaw, Poland, between 1 January 2020 and 1 August 2023.

Data collected included basic demographic information (GA, body weight, route of birth), perinatal care procedures (antenatal steroids and surfactant administration), complications associated with prematurity (BPD and NEC), presence of ductus arteriosus patency, and the type of ventilation during the initial echocardiography (ECHO).

Patients were eligible for the study based on the following inclusion criteria: GA <32 weeks, ECHO performed within the first 7 days, and inborn infants. Outborn infants, those presenting ductal dependency who were administered PGE1 after birth, or those who received paracetamol at a dose of 15 mg/kg for at least 5 days, were excluded from the study. Other exclusion criteria are listed in Tab. 1.

Consent to the use of medical data, from both electronic and paper records, was obtained from the legal guardians of all participants. The study was conducted in line with the principles of the Declaration of Helsinki and was approved by the local Institutional Review Board (AKBE/331/2023).

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Inclusion criteria	Exclusion criteria
Inborn	Outborn status or lack of data
<32 weeks of gestation	Death within the 1st month of life
Echocardiography within first 7 days	Ductal-dependent heart defects and the use of PGE1 after birth
	Administration of ibuprofen prior to the 1st echocardiography
	Ligation of PDA
	Echocardiography >7th day of life
	Treatment with paracetamol 15 mg/kg/dose 4 times a day for 5–7 days
PDA – patent ductus arteriosus.	

Tab. 1. Inclusion and exclusion criteria

METHODS

Ninety-four patients were included in the study, but only 91 were given known doses of paracetamol, which made them eligible for analysis based on the primary aim of the study. The three cases where the paracetamol doses were not known were taken into account when considering the secondary aim. The "missing data", in certain features, in Tab. 2 refer to cases not taken into consideration in the statistical analysis. The 91 patients were stratified into three groups: 25 patients who did not receive paracetamol at all (control group), 49 infants who received paracetamol at an analgesic dose of less or equal to 10 mg/kg, and 17 infants were prescribed a dose of >10 mg/kg (Fig. 1). A higher analgesic dose of paracetamol was administered to patients who exhibited pain based on the Wong–Baker Faces Pain Rating Scale or showed objective signs of pain, such as tachycardia or fluctuating heart rate, increase or decrease in blood pressure, tachypnoea, apnoea or splinting, without any other identifiable cause.

Paracetamol was administered for approximately 1 to 3 days before ECHO at doses varying from 5 mg/kg/dose to 20 mg/kg/dose. Initial echocardiography was performed within the first week of life, either due to the need for mechanical ventilation or the presence of coexisting conditions. All children that required mechanical ventilation after birth had ECHO performed within the first 2 days of life. Preterm infants born at <28 weeks of gestation had ECHO within the first 3 days, and lastly, newborns in stable condition or those born after 28 weeks of gestation typically had their ECHO performed later.

During the examination, patency was recorded, and the heart anatomy, coexisting heart defects, direction of shunting through the DA, and hemodynamic disturbances. The DA was defined as "closed" if it could not be visualized on colour Doppler flow.

All examinations were performed by clinicians who underwent appropriate training and were experienced in the technique. The ultrasound assessments were performed using a Samsung Epic or Affinity Ultrasound System with an S12-4 sector array transducer.

Characteristics	Total
Number of patients	94 (100)
GA	30
Median (IQR)	(28–31)
Weight at birth [g]	1290
Median (IQR)	(990–1,600)
Birth: • vaginal • abdominal	 23 (24.5) 71 (75.5)
PDA in 1st ECHO: • yes • no	 31 (33.3) 63 (66.7)
BPD: • yes • no • missing data	 21 (22.3) 67 (71.3) 6 (6.4)
NEC: • no • yes with perforation • yes without perforation • missing data	 78 (83) 9 (9.6) 3 (3.2) 4 (4.2)
GCs treatment (completed cycles): • 0 • 1 • 2	 40 (42.6) 8 (8.5) 46 (48.9)
Number of surfactant doses: • 0 • 1 • 2 • 3	 22 (22.4) 52 (53.3) 19 (20.2) 1 (1.1)
Type of ventilation at initial echocardiography: • spontaneous breathing • mechanical ventilation • NIV	 19 (20) 44 (47) 31 (33)
Paracetamol treatment: • control • doses ≤10 mg • doses >10 mg • missing data	 25 (26.6) 49 (52.1) 17 (18.1) 3 (3.2)
BPD – bronchopulmonary dysplasia; **GA** – gestational age; **GCs** – glucocorticoids; **IQR** – interquartile range; **NEC** – necrotising enterocolitis; **NIV** – non-invasive ventilation; **PDA** – patent ductus arteriosus. Data are shown as frequencies *n* (%), unless otherwise specified.	

Tab. 2. Characteristics of patients included in analysis

Statistical analysis

Qualitative variables were presented as frequencies with corresponding percentages. Their analysis was performed using the chi-square test with appropriate corrections depending on the size of the subgroups (two-sided Fischer's correction and Yates' correction). Continuous variables were expressed as mean with standard deviation (for normally distributed variables) or as median with lower and upper quartile values (25th–75th percentile, for non-normally distributed variables). The normality of distribution was verified using the Shapiro–Wilk test.

To analyse continuous variables, the Student's *t*-test (for normally distributed variables) or the Mann–Whitney *U*-test (for non-normally distributed variables or ordinal

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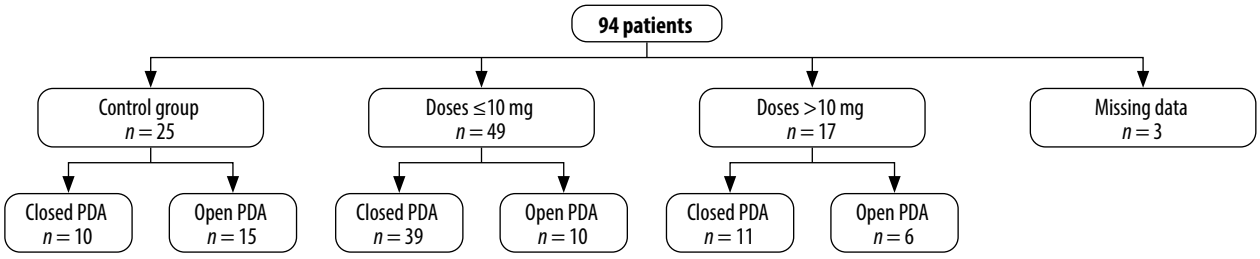

Fig. 1. Characteristics of the group according to the doses of paracetamol used

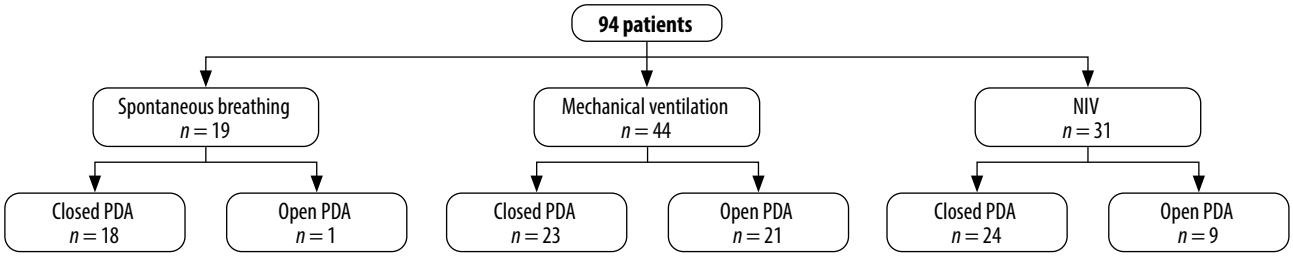

Fig. 2. Characteristics of the group according to the ventilation used

	Closed DA	Opened DA	Total	*p*-value
Weight at birth	1300	1190		0.7
GA	30	29		0.09
GA >28	50 (70.42%)	21 (29.58%)	71	0.32
GA <28	13 (56.52%)	10 (43.48%)	23	
Abdominal birth	46 (64.79%)	25 (35.21%)	71	0.58
Vaginal birth	17 (73.91%)	6 (26.09%)	23	
Paracetamol dose ≤10 mg	39 (79.59%)	10 (20.41%)	49	0.003
Paracetamol dose >10 mg	11 (64.71%)	6 (35.29%)	17	
Control	10 (40.0%)	15 (60.0%)	25	
Absence of BPD	47 (70.15%)	20 (29.85%)	67	0.22
Presence of BPD	11 (52.38%)	10 (47.62%)	21	
Echocardiography – spontaneous breathing	18 (95%)	1 (5%)	19	0.0037
Echocardiography – mechanical ventilation	23 (52%)	21 (48%)	44	
Echocardiography – NIV	22 (71%)	9 (29%)	31	
Absence of NEC	53 (67.95%)	25 (32.05%)	78	0.37
Presence of NEC	6 (50.0%)	6 (50.0%)	12	
GCs control	27 (67.5%)	13 (32.5%)	40	0.5523
GCs 1 dose	4 (50%)	4 (50%)	8	
GCs 2 doses	32 (69.6%)	14 (30.4%)	46	
Surfactant control	18 (81.8%)	4 (18.2%)	22	0.211
Surfactant 1 dose	34 (65.4%)	18 (34.6%)	52	
Surfactant 2 doses	10 (52.6%)	9 (47.4%)	19	
Surfactant 3 doses	1 (100%)	0 (0%)	1	

BPD – bronchopulmonary dysplasia; **DA** – ductus arteriosus; **GA** – gestational age; **GCs** – glucocorticoids; **NEC** – necrotising enterocolitis; **NIV** – non-invasive ventilation.
Data are shown as frequencies *n* (%), unless otherwise specified. Mann–Whitney *U*-test was used to compare weight at birth and GA between groups. For contingency tables, the Chi-squared test with appropriate corrections was used for GA, birth weight, BPD, paracetamol dose, ventilation, and NEC.

Tab. 3. Characteristics according to the presence of PDA with p*-value of performed tests*

variables) was used. Differences were considered statistically significant for p values <0.05.

Logistic regression was used to identify predictive factors for PDA presence during the initial ECHO assessment. Univariate logistic regression was performed to select predictors for the multivariate regression model. The multivariate logistic regression model construction included predictors with $p < 0.1$ in univariate analyses. All statistical analyses were performed using the Statistica 13.1 package (Tibco, Palo Alto, CA, USA).

RESULTS

The study sample comprised 94 patients at a median gestational age of 30 weeks (interquartile range, IQR: 28–31), of whom 23 (24.5%) were delivered vaginally. The median birth weight was 1,290 g (IQR: 990–1,600). During pregnancy, a total of 54 patients' mothers received antenatal steroids; specifically, 8 (8.5%) received one complete treatment cycle and 46 (48.9%) received two complete cycles. A total of 72 (77.4%) patients received surfactant treatment, while 66 patients received paracetamol. Among the surfactant-treated patients, 52 (53.3%) received a single dose, 19 (20.2%) received two, and one patient received three doses. Among the paracetamol-treated patients, 49 (52.1%) received doses ≤10 mg, while 17 (18.1%) received doses >10 mg. During ECHO, 19 (20.2%) patients exhibited spontaneous breathing, 31 (33%) required non-invasive ventilation (NIV), and 44 (47%) required mechanical ventilation (Fig. 2). During treatment, 24 cases (22.3%) of BPD, 9 (9.6%) cases of NEC, and 3 (3.2%) cases of NEC with perforation were observed. At the first ECHO, 31 (33.3%) patients had an open PDA. Among them, 15 (48.4%) patients were in the control group, 10 (32.3%) received paracetamol at ≤10 mg, and 6 (19.4%) were given doses at >10 mg (Fig. 1). Detailed characteristics of patients included in the analysis are presented in Tab. 2.

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Variable		OR	95% CI	*p*
Paracetamol treatment	Control	Reference		
	Dose ≤10 mg	0.2	0.1–0.5	0.001
	Dose >10 mg	0.4	0.1–1.3	0.12
Type of ventilation	Spontaneous breathing	Reference		
	NIV	7.36	0.9–70.4	0.07
	Mechanical ventilation	16.4	2.0–134.3	0.009
GCs treatment		1.04	0.4–2.5	0.93
GA <28 week		1.84	0.7–4.8	0.22
Surfactant		2.7	0.8–8.8	0.1

CI – confidence interval; **GA** – gestational age; **GC** – glucocorticoids; **NIV** – non-invasive ventilation; **OR** – odds ratio.

Tab. 4. Univariate logistic regression model

Variable		OR	95% CI	*p*
Paracetamol treatment	Control	Reference		
	Dose ≤10 mg	0.13	0.04–0.48	0.002
	Dose >10 mg	0.260	0.06–1.12	0.069
1st ECHO and type of ventilation	Spontaneous breathing	Reference		
	NIV	12.0	1.1–131.2	0.042
	Mechanical ventilation	12.7	1.2–137.1	0.036
Surfactant		1.5	0.3–7.2	0.611

CI – confidence interval; **NIV** – non-invasive ventilation; **OR** – odds ratio.

Tab. 5. Multivariate logistic regression model

The distribution of variables in relation to the presence of PDA is provided in Tab. 3. Paracetamol dose ($p = 0.003$) and type of ventilation during ECHO ($p = 0.0037$) were statistically significant.

Univariate logistic regression analysis showed that treatment with paracetamol at a dose equal to or less than 10 mg (OR = 0.2, 95% CI: 0.1–0.5, $p = 0.001$) was significantly associated with a reduced risk of open PDA during the initial ECHO compared to the control group. In contrast, mechanical ventilation was associated with an increased risk of open PDA compared to spontaneous respiration (OR = 16.4, 95% CI: 2.0–134.3, $p = 0.009$). No statistically significant relationship was found between open PDA and antenatal steroid treatment (OR = 1.04, 95% CI: 0.4–2.5, $p = 0.93$), GA <28 (OR = 1.84, 95% CI: 0.7–4.8, $p = 0.22$) or surfactant treatment (OR = 2.7, 95% CI: 0.8–8.8, $p = 0.1$). Detailed results are presented in Tab. 4.

All independent variables – paracetamol treatment at a dose ≤10 mg, NIV, and mechanical ventilation were statistically significant predictors of open PDA in the multivariate logistic regression model. Paracetamol at a reduced dose was related to a lower occurrence of PDA (OR = 0.13, 95% CI: 0.04–0.48, $p = 0.002$), whereas NIV (OR = 12.0, 95% CI: 1.1–131.2, $p = 0.042$) and mechanical ventilation (OR = 12.7, 95% CI: 1.2–137.1, $p = 0.044$) were significantly associated with a higher frequency of PDA. No statistically significant relationship was observed between open PDA and surfactant treatment (OR = 1.5, 95% CI: 0.3–7.2, $p = 0.611$). Detailed results are presented in Tab. 5.

DISCUSSION

Before the current study, research on the impact of paracetamol on ductal closure had yielded results comparable to those obtained with indomethacin or ibuprofen[10]. Nevertheless, the lower dose (≤10 mg/kg) continues to be a matter of debate[2,3,5,6]. The primary aim of this study was to determine whether a reduced dosage of paracetamol used for analgesia, from the first days of life, has any impact on ductus arteriosus patency. The secondary aim was to identify additional variables that might be associated with ductal patency.

In this study, patients who were treated with a low dose of paracetamol (≤10 mg/kg) had–significantly lower rates of persistent DA in the initial ECHO. These results are consistent with a few other studies on lower doses of paracetamol[15,16]. However, the relationship, even though it was observed in the group that was receiving >10 mg/kg, was without statistical significance. This might be explained by the smaller number of participants eligible for the study, thus not reaching statistical significance. Nonetheless, the study highlights that a lower dose of paracetamol is correlated with decreased patency of DA. Additionally, these results can serve as a compromise in the debate on whether or not PDA should be treated – as a lower dose can reduce the complications that are secondary to a large left-to-right shunt, without amplifying the risks that may come with the treatment of hsPDA. Moreover, it is important to note that not only paracetamol itself but also the route of its administration can affect the efficacy of PDA closure. Recent studies suggest that the oral route may be more effective in inducing ductus arteriosus contraction, compared to the intravenous route[17,18], though further studies are needed to explore this idea.

Usually, there is a tendency for later ductal closure among preterm infants – the younger the infant, the longer the duration of patency[2,3]. However, this correlation was not observed in our study. A possible explanation is that most newborns were treated with paracetamol from the early days of life, potentially masking any significant differences in GA between infants that were very preterm and extremely preterm.

The results show that there is a link between the method of ventilation and the patency of the ductus arteriosus. Newborns breathing spontaneously were the least likely to demonstrate PDA on initial ECHO – as only 5.0% of those had the DA open. Furthermore, patients undergoing non-invasive ventilation or mechanical ventilation exhibit PDA much more frequently. These findings are consistent with previous studies suggesting that PDA is rare in infants without respiratory support and that low lung compliance is strongly connected with PDA[19,20].

Ductal patency can be both a cause and result of respiratory insufficiency. Prolonged PDA with a significant left-to-right shunt may lead to an increase in capillary leakage, endothelial inflammation, and vascular remodelling. These

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changes, in turn, affects gas exchange, leading to repeated elevations of respiratory parameters such as the fraction of inspired oxygen (FiO_2) and positive end-expiratory pressure (PEEP)[21].

However, despite the beneficial effects of PEEP, such as protecting the alveoli from closing in, alleviating the infant's respiratory effort, and increasing oxygenation, it can lead to a substantial rise in pulmonary resistance that may prompt a reversal in blood flow through the DA – causing a right-to-left shunt[21,22]. This mechanism could play a part in PDA persistence in intubated newborns.

Conversely, higher saturations achieved with either NIV or mechanical ventilation can promote ductal constriction[23]. Furthermore, both MV and NIV can cause toxicity due to O_2 overexposure, leading to increased production of reactive O_2 species (ROS), which triggers the cascade of pulmonary injury and additionally increases the risk of hospital mortality[24].

In conclusion, early administration of an analgesic dose of paracetamol could decrease the risk of PDA patency. This may help prevent the overflow, caused by the PDA, into the pulmonary circulation, thus reducing the risk of pulmonary haemorrhage[22,25].

Regarding the administration of antenatal steroids, there was no significant difference in DA patency. However, steroids are known to reduce the likelihood of severe RDS by accelerating lung maturation[26]. Other studies have also shown no correlation between steroid administration and the presence of patent ductus arteriosus[27,28]. It can be speculated that, despite the obvious beneficial effects on lungs, its correlation to PDA is more intricate than typically assumed.

Exogenous surfactant is usually administered within the first 72 hours of life, and it works by decreasing the surface tension of the pulmonary alveoli. Moreover, it allows more effective oxygenation by decreasing vascular resistance within the pulmonary arteries. The mechanism should promote the closure of PDA, as it mimics the physiological process that occurs after birth. However, in the present study, the postnatal use of surfactant, like antenatal steroids, did not affect ductus arteriosus patency.

Surfactant decreases the need for high oxygen levels and PEEP ventilation parameters, but it cannot eliminate the requirement for mechanical ventilation or NIV in very and extremely preterm infants. As previously demonstrated, ventilation itself increases the likelihood of DA patency due to the physiological mechanisms involved. Our findings are contradictory to those stating that surfactant administration decreases the likelihood of PDA[29]. However, our results are in line with those studies that show a connection between artificial ventilation and ductus patency[22,25].

Despite numerous studies indicating that DA patency leads to a higher incidence of BPD[7], no such association was observed in this study. However, this may be due to the presence of other factors that play crucial roles in BPD development or inhibition of its progression that were not taken into account in the study – such as parenteral nutrition, diuretics, or caffeine administration[30]. Additionally, it seems that BPD is more prevalent in infants that not only have hsPDA but also exhibit persistent DA patency for longer periods[30,31]. Moreover, the presence of the ductus itself possibly may not have as detrimental effects as its combined effect with tracheal intubation and mechanical ventilation[31]. Nevertheless, in the present study most infants had their ductus closed or in the process of closing within the first week of life, thus probably indirectly decreasing the chance of BPD being caused by large and lasting shunts.

Moreover, in this study, the occurrence of NEC was not dependent on the presence of ductus arteriosus. However, this may be because NEC is more frequent in patients with ductal dependency, where the steal phenomenon is usually present[32]. It is important to emphasise that prenatal glucocorticoid (GC) administration, early antibiotic use, and breastfeeding also influence the risk for necrotizing enterocolitis, in addition to the presence of a patent ductus[33]. Therefore, the results should be interpreted with caution, as they should not be analysed on their own or in isolation from other risk factors that might have been present.

The study has certain limitations, as it was a single-centre retrospective study. Therefore, due to its retrospective nature, not all variables could be controlled – these include variations in the number of participants in each group, differing numbers of doses of paracetamol administered among patients, and a similar, albeit not precise, day on which the initial ECHO was performed. Strengths of the study include the ability to identify various factors that may affect DA, a sufficient sample size involving very and extremely preterm infants to achieve statistical significance through univariate and multivariate regression, and the potential for the findings to serve as a foundation for future investigations into paracetamol use at low doses. Additionally, a prospective randomized study of the effect of paracetamol in analgesic doses on ductus arteriosus should be carried out. The study could be tailored to specific exposures, such as the exact duration and doses of paracetamol administration, ECHO before the first paracetamol dose, continuous monitoring of PDA patency, and last but not least, the potential side effects of paracetamol use in preterm infants, despite its established safety profile.

CONCLUSIONS

Very and extremely preterm infants treated with paracetamol at lower doses (≤10 mg/kg/dose) had less frequent open ductus arteriosus. Furthermore, the method of ventilation affects ductus patency – with the highest likelihood of PDA when using mechanical ventilation and the lowest with spontaneous breathing. However, it is crucial to emphasise that paracetamol may not be effective in every case, as preterm infants on artificial ventilation may not benefit from its additional effects.

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Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: MMB, MZ, KK. Collection, recording and/or compilation of data: MMB, MZ, MM, KK. Analysis and interpretation of data: GM, DM. Writing of manuscript: MMB, MM, KK. Critical review of manuscript: MZ, JK. Final approval of manuscript: MZ, JK, BBD, BKN.

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