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Evaluating the Effect of Prophylactic Acetaminophen in the Prevention of Patent Ductus Arteriosus (PDA) in Premature Neonates: A randomized clinical trial

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Abstract

Background: Patent Ductus Arteriosus (PDA) can cause serious clinical consequences in premature neonates. The purpose of this study is to determine the efficacy of prophylactic parenteral acetaminophen as a safer alternative drug for PDA in preterm infants.

Methods: In a randomized clinical trial carried out in a one-year period, 60 preterm newborns under 30 weeks of gestational age with birth weights under 1500 grams, admitted in neonatal intensive care unit (NICU) of Emam Reza Hospital, Mashhad were studied. The prophylaxis group received parenteral acetaminophen for 3 days. Echocardiography was performed 96 hours after the last given dose and on the 14th day in both groups.

Result: There were 30 newborns in each group. In the 4th-day echocardiography, in 33.3% of the prophylaxis group and 26.7% of the control group, the ductus arteriosus was closed (P=0.106). In the 14th-day echocardiography, the ductus was closed in 63% and 41.4% of the intervention and control group, respectively, which was not statistically significant. In addition there was not a significant difference in the ratio of left atrium to aortic root between the two groups.

Conclusion: This study showed that in total, PDA was closed in more cases in the intervention group compared to the control group but the difference was not statistically significant. Acetaminophen is a new medicine for PDA closure, which may be more prevalent in future due to its cost effectiveness and safety.

Key Words: Acetaminophen, Ductus Arteriosus, Newborns, Paracetamol, Prophylaxis.

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1- INTRODUCTION

The ductus arteriosus, which connects the pulmonary artery to the aorta, is a vital structure during fetal life. The ductus arteriosus closes functionally during the first days of birth but anatomically at the end of the first week (1) .Thus, the entire volume of the right ventricle enters the pulmonary artery (2). Spontaneous closure of this duct occurs only in one third of low birth weight infants in the first four days of life and it remains open in 20 to 30% in infants under 32 weeks to 60% in infants under 28 weeks and is also twice as common in females as in males. This condition, known as patent ductus arteriosus (PDA), can cause serious clinical consequences and is one of the main factors affecting the survival of premature infants (3, 4) and, therefore, the vast majority of these neonates are candidates for conservative, medications, or surgical interventions (1).

Small PDA, may not cause complications, but large untreated ducts may cause complications such as a left-to-right shunt; as a result, it requires more mechanical ventilation, and may cause disorders such as bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) and even death (5). Therefore, prevention and treatment of PDA reduces mortality and morbidity and reduces neurodevelopmental complications (2). Ibuprofen and indomethacin, which are non-selective cyclooxygenase inhibitors, are among the most common drugs that have been used to prevent and treat PDA, and have been successful in 70-80% of cases. However, these drugs cause side effects such as peripheral vessels constriction and reduction of blood flow to organs, possibly, leading to dysfunction of kidneys and gastrointestinal (GI) system, reduction of platelet accumulation, and hyperbilirubinemia. Therefore, there is a need for alternative drugs to prevent this disorder in premature infants. Recently, acetaminophen or paracetamol has been considered as an alternative drug to prevent PDA (5). So far, this medicine has been the best option for pain control in neonates (6). A number of studies have shown the effectiveness of this drug in closing PDA, with fewer side effects than indomethacin and ibuprofen (7, 8). This drug is a peroxidase inhibitor and, therefore, its effect on the arterial duct is related to the inhibition of the peroxidase component of the prostaglandin synthase enzyme (7). It seems that due to less side effects and lower cost, this drug can be a good alternative for the prevention of patent ductus arteriosus (7). However, the effectiveness of this drug has not yet been extensively investigated in clinical trials, and, thus, it is not yet possible to conclude with certainty whether acetaminophen can be used as a primary drug in the prevention of patent ductus arteriosus or not. Although there have been several studies on the therapeutic role of acetaminophen in patent ductus arteriosus, few studies have been done on the preventive role of this drug. Therefore, we decided to conduct this clinical trial to understand more about the preventive effects of this drug in the improvement of preterm infants' health.

2- MATERIAL AND METHOD

2-1. Design and participants

In this randomized clinical trial, the participants included 60 premature neonates with gestational ages (GA) less than 30 weeks and weighs less than 1500 grams who were admitted to the neonatal department of Imam Reza Hospital in a one-year period. The exclusion criteria included: neonates with congestive heart failure, Presence of liver or kidney disease or cholestasis, Presence of congenital heart disease, Persistent Pulmonary Hypertension of the Neonate (PPHN),

Genetic disorder and congenital malformations, 5-minute Apgar score less than 5, umbilical pH < 7.2, septicemia, the patient illness and a difference, more than 3%, in pre-ductal and post-ductal oxygen saturation.

2-2. Intervention

After obtaining informed consent from parents, infants were randomly divided into intervention (30 patients) and control (30 patients) groups. A Single-blind randomization was done by sealed envelopes. Neonates in the intervention group received parenteral acetaminophen at a dose of 10 mg/kg every 6 hours for three days. The first dose was administered after 12 hours of birth to provide enough time to examine the newborn for underlying cardiac pathology. Infants in the control group (no placebo) did not receive preventive medication (they would be treated if symptomatic PDA develops).

2-3. Measuring Tools

All included patients were clinically examined daily for PDA symptoms and findings. If they were symptomatic, they underwent echocardiography, and if there were no symptoms, they were all subjected to echocardiography on the 4th day of birth, and examined for the presence of PDA (ductal size and the ratio of left atrium to aortic root; LA/AR). The relevant information (demographic information, pregnancy history, echocardiography findings and secondary outcomes) were recorded in a pre-designed checklist. Infants who had symptomatic PDA, received paracetamol or ibuprofen (if there was no response to paracetamol) with a therapeutic dose. If there is a change in the general condition and liver dysfunction (which is determined in clinical symptoms), the administration of acetaminophen was stopped; and the infant was excluded from the study. Finally, the data was collected and statistical analysis was done, using SPSS software. The secondary outcomes of these patients included the following: evaluating for bronchopulmonary dysplasia (BPD) at the age of 36 weeks of pregnancy or in the time of discharge (the one which comes first), through the oxygen saturation test (with the need of 21 % oxygen in mild type, less than 30% oxygen in the moderate type and more than 30% oxygen in the severe type), Intraventricular Hemorrhage (IVH) through serial ultrasound of the brain on a weekly basis, Necrotizing Entero-Colitis (NEC) based on clinical symptoms, Retinopathy of Prematurity (ROP) in one month through retinal observation with Ret Cam, sepsis at any time (based on clinical and laboratory symptoms) and finally death.

2-4. Data Analyses

After collecting the study data, it was entered into SPSS software and relevant statistical analyzes were performed. Descriptive findings were reported in the form of tables and graphs using appropriate dispersion and centrality indices. Mean and standard deviation were used to describe quantitative data with normal distribution, and median and quartile range were used for data with non-normal distribution. Frequency (percentage) was used to describe qualitative data. In order to compare qualitative variables, Chi-square test or Fisher's exact test was used. If necessary, unpaired t-test or its non-parametric equivalent (Mann-Whitney) was used to compare quantitative variables. In order to evaluate the effect of confounding factors on the main variable under study, if needed (significance of confounding factors), a suitable regression model was used. A significance level of less than 0.05 was considered in all calculations.

3- RESULTS

This study was carried out as a clinical trial on 60 premature infants under 30 GA and under 1500 grams, who were

randomly divided into an intervention (30 people) and a control (30 people). Of the 60 patients studied, 37 (63.7%) were male. 49 patients (87.7%) were born by cesarean section (CS). Some other basic information is presented in **Table 1**. The average duration of hospitalization in the control group was more than that of the intervention group, but there was no significant difference between the two groups. (33/76 ±16/56 vs. 28/66 ±17/50 days) (P-value=0.251) (**Table 1**).

Table-1. Baseline characteristics of the patients

Variables		Total population	Intervention	Control	p-value
Qualitative		N (percent)	N (percent)	N (percent)	
Gender (male)		37(61.7%)	18(60%)	19(63.3%)	0.791*
Cesarean Section(CS)		49(87.7%)	24(80%)	25(83.3%)	0.739*
Maternal Disease	GDM [1]	6(10%)	5(16.7%)	1(3.3%)	0.195†
	Preeclampsia	9(15%)	5(16.7%)	4(13.3%)	>0.9 †
	Thyroid Disease	6 (10%)	0	6(20%)	0.024 †
	PROM [2]	15(25%)	8	7	0.766*
	Quantitative	Mean (SD) [3]	Mean (SD)	Mean (SD)	-
	GA [4]	28.2 ±1	28.3 ± 0.987	28.26 ±1	-
	APGAR min 1	5.2 ± 2.26	5.9±1.73	4.5 ±2.5	-
	APGAR min 5	7.6 ± 1	7.96 ± 0.927	7.40 ±1.19	0.065
	Birth Weight	1120.16 ±199.47	1167.5 ±181.2	1086.66 ±213.9	0.196
	Hospitalization Day	31.2 ±17.08	28.66 ±17.50	33.76 ±16.56	0.251

N: Number, *: Pearson chi-square test, †: Fisher's Exact Test
[1] GDM: Gestational Diabetes Mellitus
[2] PROM: Premature Rupture of Membrane
[3] SD: Standard Deviation
[4] GA: Gestational Age

In the echocardiography that was performed on the 4th day of birth, the ductus was closed in 10 people from the intervention group (33.3%) and 8 people from the control group (26.7%), which was not statistically significant (P-value = 0.106). The duct size in most patients in both groups was small (50% in the intervention and 53.3% in the control group). And in the rest, the duct size was medium. The ratio of left atrium to aortic root was 1.1 (1.2-1.2) in the intervention group and 1.2 (1.2-1.2) in the control group, which were not significantly different.

In the echocardiography, which was repeated on the 14th day of birth, the ductus was closed in 17 cases from the intervention group (63%) and 12 controls (41.4%), which were not significantly different. 2 patients in the intervention group had ducts with large size. The statistical result in terms of other echocardiographic parameters was similar to the examination on the 4th day of birth (**Table 2**). PDA was not reopened in any of the previously closed patients.

In the intervention group, 15 people (50%) and in the control group, 17 people (56%) needed treatment (medication or conservative) due to symptomatic PDA. In the intervention group, 5 people needed to receive a therapeutic dose of acetaminophen (53.3%).

Table-2: Echocardiographic findings of the two groups

Variable	Total population N (percent)	Mean ± SD	Intervention	Median (25-75 percentile)	Control	Median (25-75 percentile)	P-value
4th day Echo, ductal diameter	-	0.91 ± 0.683	-	1.05 (0-1.4)	-	1.2 (0-1.4)	0.841 †
Close	18 (30 %)	-	10 (33.3%)	-	8 (21.7%)	-	0.573
Open	-	-	-	-	-	-	-
Small	31(57.7%)	-	15 (50%)	-	16 (53.3%)	-	-
Moderate	11 (18.3%)	-	5 (16.7%)	-	6 (20%)	-	-
Large	0 (0%)	-	0 (0%)	-	0 (0%)	-	-
14th day Echo, ductal diameter	-	0.63 ± 0.787	-	0 (0-1.1)	-	0.8 (0-1.1)	0/093*
Close	29(51.8%)	-	17 (63%)	--	12 (41.4%)	-	0.106
Open	-	-	-	-	-	-	-
Small	20 (35.7 %)	-	6 (22.2%)	-	14 (48.3%)	-	-
Moderate	5 (8.9%)	-	2 (7.4%)	-	3 (10.3%)	-	-
Large	2 (3.6%)	-	2 (7.4%)	-	0 (0%)	-	-
4th day echo, a/A [1]	-	1.1 ± 0.194	-	1.1 (1-1.2)	-	1.2 (1-1.2)	0/837†
Small	30 (50 %)		14 (46.7%)	-	16 (53.3%)	-	-
Moderate	12(20 %)	-	6 (20 %)	-	6 (20%)	-	-
Large	0 (0%)	-	0 (0%)	-	0 (0%)	-	-
14th day echo, a/A #	-	1 ± 0.237	-	1 (1-1.1)	-	1.1 (1-1.2)	0.093*
Small	20 (35.7%)	-	6 (22.2%)	-	14 (48.3%)	-	-
Moderate	5 (8.9%)	-	2 (7.4%)	-	3 (10.3%)	-	-
Large	2 (3.6%)	-	2 (7.4%)	-	0 (0%)	-	-

#: Valid percent because of missing data (4 patients died before 14 day of age)
†: Fisher's Exact Test, *: Pearson chi-square test
a/A: ratio of left atrium to the Aortic root

2 patients needed to receive ibuprofen with a therapeutic dose due to lack of response to acetaminophen, and one patient needed surgery. 5 patients also responded to supportive treatment. In the control group, 12 people (70.6%) needed to receive acetaminophen, one person received treatment with ibuprofen (5.9%) and 4 patients (23.5%) also received supportive treatment. In total, there was no significant difference between the two groups in terms of the need for treatment (P-value>0.05) (**Table 3**).

Table-3: treatment need after acetaminophen prophylaxis

Variable (N, %)	Total population#	Intervention	Control
Acetaminophen	20 (62.5 %)	8 (53.3 %)	12 (70.6%)
Ibuprofen +Acetaminophen	2 (6.3 %)	1 (6.7 %)	1 (5.9%)
Ibuprofen +Acetaminophen + Surgery	1 (3.1 %)	1 (6.7%)	0 (0%)
Conservative	9 (28.1%)	5 (33.3%)	4 (23.5%)

#: Valid percent

In the follow-up, Retinopathy of prematurity and sepsis in the control group were more than the intervention group (20% vs. 6.7% in retinopathy and 43.3% vs. 20% in sepsis). But it was not statistically significant (P>0.05). In addition, there was no significant difference in the incidence of other secondary outcomes presented in **Table 4**.Four patients in the control group had positive cultures for sepsis. Finally, Mortality was 20% in the intervention group and 23.3% in the control group, which was not significantly different between the two groups (P-value = 0.766) (**Table 4**).

Table-4: Comparison of secondary outcomes between the groups

Variable. N, %	Total population	Intervention	Control	P-value
IVH	15 (25)	7(23.3)	8 (26.7)	0.766*
NEC				0.938†
Suspected	18(30)	9(30)	9 (30)	
Definite	9 (15)	4 (13.3)	5 (16.7)	
Advance	1 (1.7)	0 (0)	1 (3.3)	
BPD				0.716*
Mild	11 (18.3%)	6 (20%)	5 (16%)	
Moderate	12 (20)	7 (23.3)	5 (16.7)	
Severe	2 (3.3%)	1 (3.3%)	1 (3.3%)	
ROP	8 (13.3%)	2 (6.7%)	6 (20 %)	0.254†
Sepsis	19 (31.7)	6 (20%)	13 (43.3%)	0.052*
BC +#	4 (23.5%)	0 (0%)	4 (23.5%)	0.237
Mortality	13 (21.7%)	6 (20%)	7 (23.3 %)	0.766*

#: valid percent, *: Pearson chi-square test, †: Fisher's Exact Test

4- DISCUSSION

In our study, we have used parenteral acetaminophen to prevent PDA in premature newborns less than 30 GA. So far, few studies have been conducted in this field, most of which have shown the positive effect of this drug in preventing PDA (2, 7, 9, 10). In the present study, we have used a lower dose of acetaminophen (10 mg/kg every 6 hours for three days) than most previous studies.

In terms of the average duration of hospitalization, it was more in the control group than the intervention group, but similar to the study conducted by Bagheri et al (2), no significant statistical difference was observed.

According to available scientific sources, the ductus arteriosus remains open in 30-

60% of premature neonates (1). In our study, in echocardiography on the 4th day of birth, 66.3% in the intervention group and 73.3% in the control group, the ductus arteriosus remained open. In this regard, as well as in other echocardiography findings, no significant difference was found between the two groups. In the echocardiography repeated on the 14th day of birth, the duct remained open in 37% in the intervention group and 58.6% in the control group. The duct size was reported to be small (less than 1.5 mm) in both groups and in both periods of echocardiography. Although, on the 14th day of birth, more ducts were closed numerically in infants of the intervention group, there was no statistical difference. In a study conducted by Akbari et al., in 2015 and on 32 babies under 32 weeks, acetaminophen was administered orally at a dose of 15 mg/kg every 6 hours for two days, the ductus arteriosus remained open in 50% of the controls and 25% of the intervention cases, , which was not a significant difference. This result can be due to the small sample size and shorter prophylaxis period (3). However, in another study by Hook et al., in 2020, who administered acetaminophen at the same dose as ours for 5 days, the prevalence of PDA was statistically lower in the intervention group. Of course, in their study, the sample size (476 patients) and duration of acetaminophen administration were larger than ours. Also, in their study, neonates under 28 weeks were not studied (5). In another study in Shahrekord in 2021, where acetaminophen was given with the same dose as our study, an increase in ductus arteriosus closure was reported in the intervention group. In their study, acetaminophen was prescribed for a longer period than ours (5 days instead of 3 days) (1). In another study conducted by Aikio et alIn 2008 to 2011 on 160 infants under 32 weeks of age, acetaminophen was clearly associated with a reduction in the prevalence of open ductus arteriosus from 30.7% to 14.7% (10). Also, in another study conducted by Harkin et al., in 2016 on 63 premature neonates under 32 weeks, faster closure of the ductus was reported in the paracetamol group (11). In both of these studies, paracetamol was administered at a dose of 20 mg per kg and then 7.5 mg every 6 hours which was higher than that of our study. Also, in another study by Bagheri et al., in 2018, which was conducted on 160 babies under 34 weeks, the prevalence of ductus arteriosus in the intervention group was clearly reduced (2). However, this result could be due to the greater gestational age of the patients in their study as compared to ours. In another study conducted by Asadpour et al., in 2021, after the intervention, 50% infants had open ductus arteriosus in the control group and 15% in the intervention group, which indicated the effectiveness of acetaminophen (1).

In our study, after the intervention, 15 patients in the intervention and 17 in the control group had symptomatic open ducts that required treatment. We administered acetaminophen as the first treatment choice with a therapeutic dose (15 mg per kg every 6 hours for 3 days) due to fewer side effects, and if there was no response to it, oral ibuprofen with a therapeutic dose (10 mg per kg on the first day and then 5 mg daily up to 3 days) was an alternative. In Akbari et al.'s study in 2015, the first choice of treatment was ibuprofen, and the intervention group required less treatment than the control group (18.8% vs. 37.5%) (3). Also, in Asadpour et al.'s study, the first choice was ibuprofen, and the intervention group responded better to ibuprofen (1).

In our study, both groups responded well to the therapeutic dose of acetaminophen, and there was no difference between the two groups in terms of the need for treatment with the second drug (ibuprofen) (6.7 % in the intervention group and 5.9% in the control group). One person in the

intervention group needed surgery due to lack of response to acetaminophen and ibuprofen. In Aikio et al.'s study, paracetamol reduced the need for ibuprofen treatment and reduced the need for surgical closure of the duct (10). In a study conducted in 2020 in Austria, 12.2% needed treatment with ibuprofen due to lack of response to acetaminophen (5).

In the follow-up of our patients, prophylactic acetaminophen had no effect on reducing the prevalence of IVH, BPD, and NEC. One reason could be that these cases are affected in the presence of other factors such as maternal, neonatal and environmental factors (2). Although in the case of retinopathy of prematurity and delayed sepsis, the number of people involved in the intervention group was lower, there was no difference in terms of statistical analysis. Similarly, positive culture sepsis was reported only in the control group, but due to the limitations of the culture environment, it cannot be relied upon.

In the study conducted by Silahi et al., in 2020, even though it was conducted with a higher dose and larger sample size, similar results were reported. Of course, the prevalence of grade 3-4 intraventricular hemorrhage had decreased (9). On the other hand, in Hook's study in 2020, where acetaminophen was prescribed with a dose similar to ours but with a much larger sample size than ours, a decrease in the prevalence of moderate to severe bronchopulmonary dysplasia and a decrease in retinopathy and delayed sepsis were reported in the intervention group, but there was no effect in terms of reducing intraventricular hemorrhage and necrotizing enterocolitis (5).

Finally, the mortality in our entire population was 13%, which was higher than other studies and there was no significant difference between the two groups (20% in the intervention and 23.3% in the control group). One of the causes of higher mortality in our study could be that the participants of the study had a lower gestational age than other studies and thus had more complications of prematurity. In Silahi's study, which only included infants under 28 weeks, the mortality percentage in two groups was higher than that in our study (42.3% in the intervention group and 57.7% in the control group) (9). In other studies, there was no reduction in mortality in the intervention group.

In our study, injectable acetaminophen was administered with a dose lower than that recommended in the articles (12). And liver complications were not reported in studies with higher doses. As a result, the possibility of complications in our study was very low and no cases were reported. For this purpose, in order to reduce blood sampling and reduce unnecessary costs, complications were examined in the form of examinations and clinical evidence.

4-1. Limitation and strength

The limitations of our study included relatively small sample size, lack of longer follow-ups in terms of evolution, and not evaluating the ventilator need duration. The strengths of our study include investigating the effect on other complications of prematurity, the absence of frequent blood sampling, reviewing the results of echocardiography on both 4th and 14th days.

5- CONCLUSION

This study revealed that in total, PDA was closed in more cases in the intervention group compared to the control group but it was statistically insignificant. Acetaminophen as a new strategy for PDA closure may be used in future because of its safety and lower cost. However, further studies with larger sample sizes and higher doses are needed to show the efficacy of acetaminophen, side effects, and complications in PDA prophylaxis treatment.

6- ETHICAL CONSIDERATIONS

The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences (ID-code: IR.MUMS.MEDICAL.REC.1401.328), and registered at Iranian Registry of Clinical Trials (IRCT: 20081021001378 N15).

7- ACKNOWLEDGEMENT

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8- REFERENCE

1. Asadpour N, Choupani R, Kermani M, Salehifard A. The Effects of Acetaminophen Prophylaxis on Patent Ductus Arteriosus Closure in Premature Infants: A Clinical Trial Study. Int J Pediatr. 2021 9(7):14077-83.

2. Bagheri MM, Bahman-Bijari B, Torabi-Nejad MH, Niknafs P, Mousavi H, Sabzevari F, Kheradmand-Sarokolai Z, Azizzadeh F. Is Prophylactic Parenteral Paracetamol Effective to Diminish Incidence of PDA in Preterm Neonates? A Randomized Trial. Iran J Pediatr. 2018:e11735.

3. Asbagh PA, Reza M, Zarkesh, Nili F, Nayeri FS, Naeem AT. Prophylactic treatment with oral paracetamol for patent ductus arteriosus in preterm infants: a randomized clinical trial. Tehran Univ Med J. 2015 73(2):86-92.

4. Terrin G, Conte F, Oncel MY ea. Paracetamol for the treatment of patent ductus arteriosus in preterm neonates: a sys- tematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2016; 101:127-36.

5. Höck M, Brunner B, Rier V, Thöni S, Trawöger R, Geiger R, Schermer E, Karall T, Kiechl-Kohlendorfer U. Prophylactic low-dose paracetamol administration associated with lowered rate of patent ductus arteriosus in preterm infants e Impact on outcome and pain perception. Pediatrics and Neonatology. 2020; 61:84-91.

6. Anker JNvd, K. Allegaert. Acetaminophen to Prevent Symptomatic Patent Ductus Arteriosus: Another Drug Bites the Dust? J Pediatr. 2016; 177:7-9.

7. Puig AMH. Efficacy of intravenous paracetamol compared to placebo in the prevention of patent ductus arteriosus in very preterm newborns. 2017.

8. Samadi M, Nabaee Z, Mostafagharebaghi M, Mahalei M, Sheykhsaran E, K. M. Oral acetaminophen administration for patent ductus arteriosus (PDA) closure in preterm neonates. Med J Tabriz Uni Med Sciences. 2021; 43(3):254-9.

9. Musa Silahli, Zeynel Gokmen, Tekin M. Prophylactic intravenous paracetamol use in extremely premature infants for patent ductus arteriosus. J Basic Clin Physiol Pharmacol. 2020:20200006.

10. O. Aikio, P. Harkin, T. Saarela, Hallman M.

Early paracetamol treatment is associated with lowered risk of persistent ductus arteriosus in very preterm infants. J Matern Fetal Neonatal Med. 2014; 27:1252-6.

11. Härkin P, Härmä A, Aikio O, Valkama M, Leskinen M, Saarela T, Hallman S. Paracetamol Accelerates Closure of the Ductus Arteriosus after Premature Birth: A Randomized Trial. J Pediatr. 2016; 177:72-7.

12. Allegaert K, Palmer GM, BJ A. The pharmacokinetics of intravenous paracetamol in neonates: size matters most. Arch Dis Child. 2011; 96:575e80.