Intravenous paracetamol (acetaminophen) for patent ductus arteriosus closure in premature infants ≤ 32 weeks' gestation

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Abstract

Objective: To identify the effectiveness of intravenous paracetamol for closure of patent ductus arteriosus in preterm ≤ 32 weeks gestation. **Method:** This was a series of cases, a therapeutic intervention to closure was applied for ductus arteriosus >2 mm, identified by echocardiogram after 3 days of life, intravenous paracetamol was used, for a time range from 3 up to 6 days. **Results:** The prevalence of patent arteriosus in ≤ 32 weeks gestation, was 40%. 21 patients were included, there was a predominance of female. Average age at diagnosis was 29 weeks gestation. The minimum weight 750 g, maximum 1350 g. Echocardiogram corroborated closure in 76%, intravenous paracetamol was more successful with 6 days treatment. **Conclusions:** The prevalence of patent ductus arteriosus is directly proportional to the gestational age, being more common in women. Successful closure was 76%, this drug shows to be as effective as the first-choice drug, and a good alternative for intravenous therapy.

KEY WORDS: Acetaminophen. Patent ductus arteriosus. Premature infant.

Introduction

Patent ductus arteriosus (PDA) is the persistence of a duct that connects the pulmonary artery with the descending aorta¹. Its incidence is inversely related to gestational age and weight, and it is more common in premature infants²; PDA has been estimated to occur in 53% of newborns < 33 weeks of gestation (WOG)³. In 67% of preterm newborns (PTNBs) weighing between 1000 and 1500 g will their ductus arteriosus spontaneously close by the seventh day of life⁴. On the other hand, spontaneous closure only occurs in 30-35% of PTNBs weighing < 1000 g⁵.

PDA is strongly associated with trisomy 21, 18 and 13 and with other conditions such as the CHARGE, Noonan and Holt-Oram syndromes, as well as with congenital rubella⁶.

Treatment can include ventilation and fluid control general measures, use of cyclooxygenase inhibiting drugs or surgical closure⁷.

In the PTNB, a ductus arteriosus larger than 2.2 mm at third day of life predicts spontaneous closure failure and suggests the need for early treatment, especially when associated with clinical signs⁸. In addition, prophylactic treatment for ductus arteriosus closure reduces the incidence of intraventricular hemorrhage and decreases the need for surgical treatment⁹. Among the medications of choice, ibuprofen is as effective as indomethacin for PDSA closure, with ibuprofen, either by intravenous or oral route, being the ideal choice so far, since it reduces the risk for necrotizing enterocolitis and transient renal insufficiency¹⁰. Both indomethacin and ibuprofen promote ductal closure in 70-80% of cases¹¹.

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Recently, paracetamol has been shown to be as effective as ibuprofen for PDA closure in preterms^{12,13}. The paracetamol dose used for PDA closure is 15 mg/kg every 6 hours for 3 to 7 days¹³.

Method

PTNBs of ≤ 32 weeks of gestation (WOG), in whom > 2 mm PDA at its pulmonary end was identified by transthoracic echocardiogram, with an absence of ductus arteriosus closure pathways being demonstrated by Doppler spectrum, in all cases with a significant size, i.e. with a ductus/aorta ratio > 0.5 and variable degrees of left cavities dilation, were included. Performance of these assessment was avoided prior to 3 days of life. Patients with more than one heart defect or complex heart pathology, as well as seriously ill patients, with platelet counts below 100,000, with renal or hepatic conditions or with presence of active bleeding were excluded. The selected cases underwent therapeutic intervention with intravenous paracetamol at a dose of 15 mg/kg every 6 hours, for 3 to 6 days. Once treatment was started, follow-up involved making the first assessment at 72 hours and a second one at treatment completion, with it being discontinued in case closure was identified at first assessment. Success was considered as ductus arteriosus complete closure. The analysis of results was carried out with the SPSS v21 software.

Results

Of total live births on that year (9102), approximately 8% required hospitalization (728 patients/year), with PTNBs accounting for 52.2% ($n = 380$); out of these, 150 were ≤ 32 WOG, and 40% had PDA ($n = 60$), with 21 patients meeting the inclusion criteria (Fig. 1). There was predominance of the female gender, at a 2.5:1 ratio. Average age at diagnosis was 29 WOG, with a range of 26-32 WOG. Average age at detection was 8 days, with a range of 3-20 days. The ductus arteriosus minimum diameter was 2.0 mm, and its largest size at its pulmonary edge was 3.2 mm, with a median of 2.5 mm. In 100 of cases, the ductus/aorta ratio was > 0.5 , with left cavities' varying degrees of dilation, as well as an absence of closure pathways in the Doppler echocardiography. Documented weight was 1027 g on average, with a minimum of 750 g and a maximum of 1350 g (Table 1).

The administered treatment was paracetamol by intravenous route at the described dose of 15 mg/kg every 6 hours for 3 to 6 days, with PDA closure being

Figure 1. General description of the follow-up of patient carriers of patent ductus arteriosus (PDA). NB: newborns; WOG: weeks of gestation.

identified in 5 of the 21 patients with the 3-day regimen and in 11 patients more at the completion of 6 days of treatment. Finally, PDA closure, corroborated by echocardiogram, was achieved in 16 patients, which translates into 76% (Table 1).

With regard to treatment outcome according to patient gender, greater success is proportionally appreciated in the female (80%) than in the male gender (66%), although the difference has no statistical difference (Table 2).

A higher percentage of closure success, of up to 89%, was found in patients weighing < 1 kg, in comparison with those weighing > 1 kg, in whom closure was achieved in 69% (Table 3). In those who had < 30 WOG, better percentage of closure is equally identified, of up to 81% ($n = 13$) (Table 4).

Discussion

In this review, ductus arteriosus patency was identified in 40% of cases, which is slightly lower than the frequency reported in other series³.

A follow-up was made of conducts < 2 mm, and of these patients, two third parts (67%) experienced spontaneous closure around the first week of life, just as reported by other authors⁴.

In the patients with PDA > 2 mm, in view of the low probability of closure⁵, the decision was made to start an early treatment, i.e. even prior to observing overt manifestations of heart failure, thereby looking for less ductus arteriosus patency, lower hemodynamical impact and less surgical closure requirements⁷.

The most affected gender in our series were females, at a 2.5:1 ratio, which is a trend that had already been reported in other reviews¹⁴.

Table 1. General information of patients included in the study

N	WOG	Weight	Gender	Age	PDA	PDA/Ao >0.5	Tx days	Closure	Reaction
1	26	750	M	5	2.3	Yes	6	No	No
2	27	850	F	11	2.3	Yes	3	Yes	No
3	28	890	F	5	2.0	Yes	6	Yes	No
4	28	1.050	F	3	2.3	Yes	3	Yes	No
5	28	960	M	3	2.0	Yes	6	Yes	No
6	28	980	F	3	2.3	Yes	6	Yes	No
7	29	790	F	6	2.6	Yes	6	Yes	No
8	29	950	F	9	3.2	Yes	6	Yes	No
9	29	1.130	F	3	3.0	Yes	3	Yes	No
10	29	1.120	F	3	2.5	Yes	6	Yes	No
11	29	1.050	F	20	2.1	Yes	6	Yes	No
12	29	1.070	F	10	3.0	Yes	3	Yes	No
13	30	950	M	8	2.1	Yes	6	Yes	No
14	30	1.000	F	16	3.0	Yes	6	Yes	No
15	30	1.100	F	4	2.2	Yes	6	No	No
16	30	1.100	F	6	2.8	Yes	6	No	No
17	31	1.130	M	13	2.7	Yes	6	Yes	No
18	31	1.315	F	9	3.0	Yes	6	No	No
19	32	1.350	F	7	3.0	Yes	6	Yes	No
20	32	1.000	M	14	2.2	Yes	3	Yes	No
21	32	1.050	M	14	2.5	Yes	6	No	No

F: female; M: male; PDA: patent ductus arteriosus; PDA/Ao: patent/ductus arteriosus/aorta ratio; Tx: treatment; WOG: weeks of gestation.

Table 2. Population distribution by treatment success and gender

	Ductus arteriosus closure		Total
	Success	Failure	
Female	12	3	15
Male	4	2	6
Total	16	5	21

Chi-square: 0.420; $P=0.45$.**Table 3. Population distribution according to treatment success and birth weight**

	Ductus arteriosus closure		Total
	Success	Failure	
< 1 kg	7	1	8
> 1 kg	9	4	13
Total	16	5	21

Chi-square: 0.91; $P=0.34$.**Table 4. Population distribution by success and weeks of gestation at diagnosis**

	Ductus arteriosus closure		Total
	Success	Failure	
< 30 WOG	13	3	16
> 31 WOG	3	2	5
Total	16	5	21

Chi-square: 0.94; $P=0.33$.

WOG: weeks of gestation.

We used the same dose suggested by other authors¹³, 15 mg/kg every 6 hours for 3 days, but extending treatment duration to up to 6 days was necessary for poor response within the first 72 hours (only 24% of patients had experienced closure with 3 days of treatment).

We chose intravenous treatment because, with this gestational age, some had initiation of the enteral route

Table 5. Population distribution by treatment success and PDA pulmonary edge internal diameter

	Ductus arteriosus closure		Total
	Success	Failure	
< 3 mm	11	4	12
> 3 mm	5	1	9
Total	16	5	21

Chi-square: 0.2; $P=0.55$.**Table 6. Population distribution by treatment success and age at pharmacological treatment initiation**

	Ductus arteriosus closure		Total
	Success	Failure	
< 7 days of life	7	3	10
> 7 days of life	9	2	11
Total	16	5	21

Chi-square: 0.40; $P=0.45$.

contraindicated, with closure success being found and corroborated by echocardiogram in 76% of cases, which is a figure very similar to those reported in recent reviews with the use of paracetamol by oral route¹⁰.

The statistical analysis was carried out looking for an association of different variables with the probability of pharmacological closure success, such as weight higher or lower than 1 kg, ductus arteriosus size classified as medium or large (3 mm as cutoff point), gestational age shorter or longer than 30 weeks, and patient age at pharmacological treatment initiation. None of them had a statistically significant association with the likelihood of success, most probably owing to the low number of patients included in the series (Tables 2 to 6).

Apparently, in those patients who used intravenous paracetamol there was no hepatic enzymes increase to abnormal ranges, as well as in creatinine values, but it is important mentioning that the design of the present study was not intended to look for adverse reactions.

Conclusions

The prevalence of PDA is directly proportional to gestational age, and it is more common in females.

Echocardiogram-documented closure success was 76%, with higher probability of success using a 6-day treatment regimen. Apparently, there were no immediate adverse effects with the use of this drug, which was shown to be an efficacious, safe on the short-term and accessible drug for PDA closure, which is a good alternative when avoiding the enteral route is sought.

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Conflicts of interests

The author declares not having any conflicts of interests.

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