Acetaminophen in low doses for closure of the ductus arteriosus of the premature

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ABSTRACT

Objective : **The objective of the study is to report the experience with acetaminophen in low doses as an alternative to the treatment of the ductus arteriosus of the preterm newborn.**

Materials and Methods : **Retrospective study including preterm newborns with patent ductus arteriosus who received oral acetaminophen because treatment with indomethacin had failed or is contraindicated. A dosage consisted of a first dose of 25 mg/kg and maintenance doses of 30 mg/kg/day, for 3 to 7 days. A second cycle was administered in cases of reopening of the ductus arteriosus. The rates of ductal closure and surgery were calculated. Patients were categorized into responder and nonresponder groups for acetaminophen, and the average values of ductal diameter, weight, gestational age, and postnatal age were compared.**

Results : **Eighty-seven preterm newborns, with a postnatal age from 3 to 27 days, with average values of ductus arteriosus equal to 2.5 ± 0.8 mm/kg, gestational age 27.2 ± 1.9 weeks, and birth weight 888.9 ± 241 g, received acetaminophen for 3 to 7 days. A second cycle was administered in 15 preterm newborns. The ductus closure rate, after one or two cycles, was 74.7%, and the recommendations for surgical closure were progressively reduced from 50% in the 1st year to 6.2% in the past year. Lower ductal closure rate occurred in the group of newborns with the lowest average weight ($P = 0.018$), the highest average ductal diameter ($P = 0.002$), and the lowest average gestational age ($P = 0.09$). Postnatal age at the start of acetaminophen use was shown to be irrelevant regarding the treatment ($P = 0.591$).**

Conclusions : **Acetaminophen in low doses showed to be an effective alternative for the closure of the ductus arteriosus for preterm newborns in whom treatment with indomethacin or ibuprofen failed or was contraindicated.**

Keywords : Acetaminophen, ductus arteriosus, echocardiography, indomethacin, premature

INTRODUCTION

Failure in spontaneous closure of the ductus arteriosus occurs in 50%–60% of preterm newborns with a birth weight lower than 1000 g. Such incidence is inversely proportional to birth weight and gestational age.[1-7] Aorta to pulmonary artery shunting through the patent

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ductus arteriosus (PDA) renders the preterm newborns vulnerable to pulmonary overcirculation and diminished systemic blood flow. Moreover, it is associated with significant morbidity such as failure to thrive, pulmonary edema and hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, periventricular-intraventricular hemorrhage,[2,4-11] and overall increased mortality.[2,7,12]

Conventionally, PDA medical treatment is attempted with prostaglandin-synthesis inhibitors such as indomethacin and ibuprofen, with comparable efficacy between the two drugs (up to 70%–85%).[2-7,10,11,13] Known side effects include peripheral vasoconstriction, gastrointestinal bleeding and perforation, decreased platelet aggregation, hyperbilirubinemia, and transient worsening of renal function.[2,4-9,11,14]

Surgical treatment is indicated for newborns with hemodynamically significant PDA when medical treatment fails and is associated with increased risk of bronchopulmonary dysplasia, severe retinopathy of prematurity, chylothorax, and neurosensorial lesion.[5,7,10,15,16]

Acetaminophen is also an inhibitor of prostaglandin synthesis and has been considered a promising alternative for the medical treatment of preterm newborns with PDA as a means of reducing the need for surgery. In addition, treatment with acetaminophen has achieved a success rate of nearly 80%, without significant side effects.[2-6,11,17] Most studies have evaluated a treatment regimen which consists of a daily dose of acetaminophen of 60 mg/kg of body weight,[2-6,11,17] roughly twice the recommended dosage for pain relief (30 mg/kg/day).[10,18-21] However, transient elevation of hepatic enzymes has been reported as a consequence of the increased dosage of acetaminophen.[7,21,22]

This study aims to report the experience of a tertiary care center with the treatment of PDA using low doses of acetaminophen in preterm newborns in cases where treatment with indomethacin has failed or is contraindicated.

MATERIALS AND METHODS

This observational, retrospective study was conducted between January 2012 and December 2016. In the hospital where the study was conducted, the drug of choice for pharmacological treatment (to closure) of the ductus arteriosus is oral indomethacin. Furthermore, ibuprofen is not available.

All preterm newborns who received acetaminophen for PDA closure during the study were included in the study, regardless of birth weight or gestational age. The criteria for acetaminophen usage were the presence of a large and hemodynamically significant ductus arteriosus, normal liver function (assessed by laboratory testing), and treatment failure with indomethacin or contraindications for its use. Treatment failure with indomethacin was defined as failure to achieve ductal closure after a complete cycle of indomethacin treatment. The following conditions were considered contraindications for indomethacin use: intraventricular hemorrhage, thrombocytopenia, necrotizing enterocolitis, coagulopathy or active bleeding, reduced urinary output, urea or creatinine elevation, and uncontrolled sepsis. Patients who died before treatment was complete or before final echocardiographic assessment were excluded from this study.

The first echocardiographic examination was performed between the 24th and 96th hrs of life on all preterm newborns with a birth weight <1100 g and on those with a birth weight >1100 g with a clinically suspicious PDA. Echocardiographic studies were conducted by pediatric cardiologists from the hospital where the study took place, using commercially available portable ultrasound devices. The size of the ductus arteriosus was quantified in millimeters (mm) and measured at its the narrowest point before entering the main pulmonary artery in the left parasternal short axis view. To correlate ductal width with body size, the ductus arteriosus diameter, measured in millimeters (mm), was indexed to body weight, measured in kg, yielding an index expressed in mm/kg. Patients who had a ductal diameter (mm) per body weight (kg) index > 1.5 mm/kg were considered to have a large and significant PDA.

On confirmation of normal liver function through laboratory testing, all preterm newborns who met the criteria above cited were given oral acetaminophen (acetaminophen oral solution 200 mg/mL) with the recommended dosage for analgesia.

The dosage consisted of a first dose of 25 mg/kg, followed by maintenance doses of 15 mg/kg twice daily for neonates <32 weeks' gestational age or three times daily for those >32 weeks gestational age. The duration of treatment ranged from 3 to 7 days (determined by the achievement of ductal closure detected through echocardiographic assessment). A second cycle of acetaminophen treatment was used in patients who experienced reopening of the PDA or in those who had an initial response of ductal narrowing followed by ductus enlargement after drug cessation. Echocardiographic reassessment was carried out daily and after the completion of each cycle of acetaminophen.

Statistical analysis

Patient's data were collected from medical records, and a statistical analysis was performed with the Epiinfo 7.1.1.3 software (Atlanta, Georgia, US). The data were analyzed using central tendency measures and dispersion of continuous variables. In addition,

medical and surgical treatment success rates were calculated, and patients were categorized into "acetaminophen-responder" and "nonresponder" groups. Groups' characteristics, including average ductus diameter, gestational age, body weight, and postnatal age at the onset of treatment were compared using the ANOVA test, in accordance with Bartlett's test. Statistical significance level was set at $P < 0.05$.

This study was granted approval by the Hospital's Research Ethics Committee. Informed consent for this retrospective study was waived by the Hospital's Institutional Research Board.

RESULTS

Between January 2012 and December 2016, 159 preterm newborns were identified with PDA, where pharmacologic treatment was recommended. A 108 of them were given three doses of indomethacin orally (0.2 mg/Kg, twice a day), between the 2nd and 7th day of life, achieving therapeutic success in 77 of them (71.3%). However, in seven patients (9%), the ductus arteriosus reopened. The gestational age and birth weight varied from 24:0 to 32:3 weeks (average value of 27.6 ± 1.9 weeks) and from 400 to 1520 g (average value of 855 ± 201.8 g), respectively.

Eighty-nine preterm newborns met the criteria for treatment with acetaminophen, 51 of them for having contraindications to treatment with indomethacin, and 38 for the treatment with indomethacin having failed (31 with no response and seven with reopening).

Two patients died before the final echocardiographic assessment and were excluded from the study.

Among the remaining 87 preterm newborns, the gestational age varied from 23.4 to 33.1 weeks (average value of 27.2 ± 1.9 weeks) and the birth weight varied from 470 to 1605 g (average value of 888.9 ± 241.0). The gestational age ($P = 0.145$) and birth weight ($P = 0.286$) were similar to the newborns' who were responsive to indomethacin and paracetamol.

Ductus arteriosus diameter and postnatal age at the onset of treatment with acetaminophen ranged between 1.5 and 4.8 mm/kg (average value of 2.5 ± 0.8 mm/kg) and between 3 and 27 days (average value of 10.4 ± 5.5 days), respectively. Preterm newborns with longer chronological age showed clinical and echocardiographic signs of hemodynamic repercussion as a consequence of PDA, and acetaminophen was used as an alternative to surgical treatment. The duration of the treatment with acetaminophen ranged between 3 and 7 days (average value of 4.6 ± 1.7). One patient received only the loading dose, due to a prescription mistake, and it resulted in PDA closure.

After the first cycle of treatment, the efficacy of acetaminophen therapy in inducing ductal closure was 62% (54/87), with immediate closure after drug cessation (85.2%) or in the subsequent days (14.8%). A second cycle was performed in 15 patients with a success rate of 73.3% (11/15). The overall PDA closure rate after either one or two cycles was 74.7% (65/87).

Different clinical and echocardiographic features between acetaminophen-responding and nonresponding groups such as average ductal diameter, body weight, gestational age, and chronological age at the onset of treatment are displayed on Table 1. The rate of indication for PDA surgical closure, after the acetaminophen therapy was introduced, was progressively reduced during the analyzed period, from 50% in the 1st year of the study to 6.2% in the past year [Figure 1].

No side effect was observed after the treatment with acetaminophen, and aminotransferase levels were maintained within reference limits. During treatment with indomethacin, about 10% of the newborns presented urinary volume reduction, which was normalized after the suspension of the medication.

Table 1: Clinical and echocardiographic features of acetaminophen-responding and nonresponding groups

Variables	Groups		*P* (ANOVA)
	Responding (*n*=61)	Nonresponding (*n*=26)	
Gestational age (weeks)	29.01 ± 2.36	28.09 ± 2.05	0.090
Weight (g)	926.06 ± 251	793.73 ± 191.98	0.018
Ductal diameter (mm/kg)	2.42 ± 0.81	2.98 ± 0.71	0.002
Postnatal age (days of life)	10.26 ± 5.93	10.96 ± 4.47	0.591

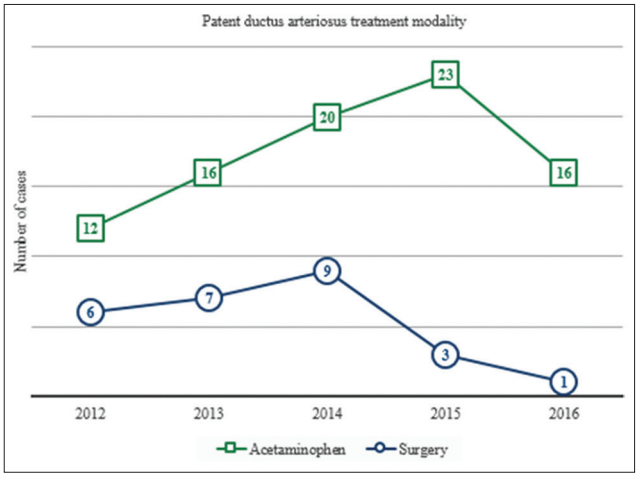

Figure 1: Need for surgical treatment in premature newborns treated with acetaminophen, by year

DISCUSSION

Therapeutic approach of the PDA in the preterm newborns has been a recurrent clinical challenge for the pediatrician and pediatric cardiologist. Any discussion of treatment modalities should acknowledge the potential morbidity associated with the PDA itself and with medical and surgical treatments. First-line treatment drugs (indomethacin and ibuprofen) have well-established side effects which lead us to perennial questioning about when and how to treat a preterm newborn with a PDA.

Hammerman *et al.*[23] reported the first case series of preterm newborns with PDA successfully treated with acetaminophen. Subsequently, many studies on this new treatment alternative have been published, with success rates comparable to those observed with indomethacin and ibuprofen use but with no reported significant side effects.[2-6,11,17] Most authors of recently published studies comparing acetaminophen to ibuprofen in the treatment of PDA have used a treatment regimen of acetaminophen in a dosage of 60 mg/kg/day divided into four doses for 3 days, with efficacy ranging from 70% to 80%.[2,3,6,17]

In this study, it has been observed that oral acetaminophen in lower doses, as recommended for pain relief – 25 mg/kg loading dose followed by a maintenance dosage of 30 mg/kg/day divided into two doses for preterm newborns <32 weeks' gestational age or divided into three doses for >32 weeks,[19] for 3–7 days – was as efficient as acetaminophen in higher doses for the closure of the ductus arteriosus. Similarly, Aikio *et al.*[9] have demonstrated that intravenous acetaminophen administered prematurely (with 13.2 ± 13.7 h of life) with the goal of pain relief in 102 preterm newborns < 32 weeks' gestational age (20 mg/kg loading dose followed by 30 mg/kg/day for 4.3 ± 3.1 days) reduced the incidence of PDA from 30.7% to 14.7% ($P = 0.008$). A clinical trial by Härkin *et al.*[14] comparing placebo to pain relief dosage intravenous acetaminophen (20 mg/kg loading dose and 30 mg/kg/day maintenance dose) has showed that the ductus arteriosus was closed earlier in the acetaminophen group (hazard ratio of 0.49; 95% confidence interval: 0.25–0.97, $P = 0.016$). Tekgunduz *et al.*[21] have reported an 83.3% (5/6) PDA closure rate with low dosage intravenous acetaminophen (30 mg/kg/day divided into three doses).

During the present study, it was observed that some preterm newborns needed a longer treatment period to achieve ductal closure, which prompted a readjustment to the treatment protocol, and treatment duration was extended to 7 days. A clinical trial by Dash *et al.*,[4] comparing the use of oral acetaminophen to intravenous indomethacin, obtained a ductal closure rate of 100% (36/36) with a 7-day treatment with acetaminophen (60 mg/kg/day). El-Khuffash *et al.*[13] have compared long (7 days) to short (2 days) courses of oral acetaminophen (60 mg/kg/day) and obtained better results with the long course. Therefore, securing a higher plasma level or longer exposition to the drug might be necessary to achieve the desired therapeutic goals.

The efficacy of indomethacin for ductus arteriosus closure is lower in preterm newborns weighing <1000 g at birth,[24] with shorter gestational age, with greater ductal diameter, and with longer postnatal age.[25] In this study, a decreased rate of PDA closure has been observed in preterm newborns with lower birth weight ($P = 0.018$), greater ductal diameter ($P = 0.002$), and lower gestational age (yet without statistical significance, $P = 0.09$). Postnatal age at the onset of acetaminophen therapy did not affect treatment efficacy ($P = 0.591$). The drug was considered effective even when administered to neonates as late as at 27 days of postnatal age.

The possibility of adverse outcomes after surgical ligation of the ductus arteriosus in premature newborns has led to a trend, in recent years, to postpone or ultimately avoid surgical treatment in this group. Acetaminophen as an alternative drug has been presented as a promising treatment option to forestall PDA surgery particularly in preterm newborns for whom treatment with traditional nonsteroid anti-inflammatory drugs such as ibuprofen and indomethacin is contraindicated or has failed. This study has confirmed the efficacy of the treatment with acetaminophen in such clinical scenarios, which lead to decreased necessity for surgical treatment.

Weisz *et al.*[15] evaluated 26 extremely premature neonates with moderate to important PDA and demonstrated that the use of oral acetaminophen (60 mg/kg/day, 3–7 days) significantly improved echocardiographic indexes of PDA hemodynamic repercussion in 12 (46%) of them, preventing surgery for these patients. Among patients who did not show echocardiographic improvement, 57% (8/14) underwent surgical treatment. Similarly, it was shown in this study significant reduction in surgical ligation of PDA after treatment with oral acetaminophen, even when using a lower dosage (30 mg/kg/day). A reduction of 90% in surgery recommendation was achieved over the past 2 years, after the duration of the treatment with acetaminophen was lengthened to 7 days.

Regarding concerns about acetaminophen-related hepatotoxicity, it has been shown that even when used in dosage twice as high as the usually recommended for analgesia in preterm newborns, there were no significant adverse effects,[2,4,6,11,17] except for a few reports of transient elevation of liver enzymes. In the present study, there was no significant elevation in aminotransferase levels either. Most of the metabolism of acetaminophen in premature neonates is carried out by sulfation, a process that yields nontoxic metabolites,

and might account for the drug's low hepatotoxicity in preterm newborns, even in those with relatively high plasma levels.[7,10,11,18,26,27] However, neonates are also able to synthesize hepatotoxic metabolites, and available literature on acetaminophen safety does not include data from extremely premature neonates and does not consider side effects caused by its use for periods longer than 2–3 days.[10,18,26] Unfortunately, a possible association between acetaminophen use and neurocognitive impairment which might lead to attention deficit disorder, hyperactivity, and autism spectrum disorders has been reported by some authors[7,28-30] and should be a reason for concern.

The retrospective data analysis, the modification of treatment protocol along the course of the studied period, and a lack of assessment regarding the long-term safety of acetaminophen use in preterm newborns were the major limitations of the present study. Nevertheless, the analysis included a significant population of extremely premature neonates, and the data were meticulously registered and retrieved because of the use of acetaminophen being considered off-label in such conditions, thus being guided by a rigorous treatment protocol.

It is possible to conclude that the treatment of PDA of the preterm newborn with oral acetaminophen in doses usually recommended for pain relief, for 3 to 7 days, has been shown to be an effective therapeutic alternative. The treatment duration should be determined by serial echocardiographic assessment to avoid prolonged and unnecessary exposition to the drug. Nonetheless, new studies on acetaminophen pharmacokinetics and pharmacodynamics are necessary to identify an optimal target concentration and therefore establish a dose that is both effective and safe in short and long terms, especially in the extremely preterm newborn.

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Conflicts of interest

There are no conflicts of interest.

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