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ORIGINAL ARTICLE

Hemodynamically unstable ductus arteriosus treated with paracetamol in a tertiary care hospital in the northeast of Mexico

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Abstract
Introduction: Patent ductus arteriosus (PDA) in premature infants after birth is associated with an increased risk of morbidity and mortality. Indomethacin or ibuprofen are the current treatments, with success rate of 70–85%, but also show severe side effects.
Objective: To demonstrate the success of intravenous paracetamol as a treatment for the hemodynamically unstable patient with ductus arteriosus closure, in a third level hospital in northeastern Mexico.
Subjects and methods: We performed a cross-sectional, observational retrospective study. All patients brought to our department between March 2013 and September 2014 were included. We also included files confirming PDA through the Yeh criteria and echocardiographic data before and after the patients took paracetamol.
Results: Twenty-four files were included in our study. 4 of them were unable to close their PDA, with paracetamol so they had to go to surgical closure. Success in closing PDA with paracetamol was 83%, and we found significant differences in the PDA measurements (2.5 [±0.8] vs. 0.8 mm [±1.1] mm, $P < 0.001$), the left atrium/aorta ratio, the right to left shunt, and ductus arteriosus/aorta ratio before and after treatment. Sepsis and bronchopulmonary dysplasia were found in 100% of patients who failed treatment, compared to 40 and 25% in the success group respectively. No side effects were present in any of the patients.
Conclusions: The use of paracetamol for ductus arteriosus closure could be effective, economical and with fewer side effects than current treatments.

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Introduction

Patent ductus arteriosus (PDA) in premature infants is linked to a greater risk of morbidity-mortality.[1,2] Incidence in premature infants is 8 per 1000 live births, and it is reported to occur in almost 80% of neonates with a weight lower than 1200 g.[3,4]

Currently, there are few pharmacological options, which are limited to cyclo-oxygenase non-selective inhibitors (COX), as well as adding liquid and diuretic restrictions to treatment.[5]

Indomethacin and ibuprofen are pharmaceuticals which promote PDA closure (with a success rate of 70–85%), with multiple side effects such as digestive tract bleeding, intestinal perforation, hyperbilirubinemia and renal failure. Thus, its use may also be contraindicated in a large population of hemodynamically unstable premature newborns, in addition to its high cost.[6]

In recent years, paracetamol has been suggested as treatment for PDA closure, since it acts in the reduction of the co-substrate for the production of prostaglandins with fewer side effects.[7–9] In our field, surgical closure is the gold standard, since the access to medications such as I.V. indomethacin and ibuprofen are limited due to import issues on behalf of suppliers. The objective of this study is to determine the efficacy of PDA in patients treated with paracetamol in a tertiary care hospital in northeastern Mexico.

Materials and methods

An observational, descriptive, retrospective study was conducted in the Neonatology Service of a tertiary care hospital in northeastern México, between March 1st, 2013 and September 1st, 2014. The study was reviewed and authorized by the institution's Ethics Committee.

A review of our files was performed, including those where diagnoses of hemodynamically unstable PDA were documented and treated with paracetamol for the period mentioned above. We included files of preterm infants at $\leq$36 weeks of gestation with clinical evidence of hemodynamically unstable PDA as the only cardiovascular diagnosis classified through the Yeh criteria and an echocardiography.[10] Amongst the Yeh criteria, there are the following parameters: tachycardia, wide pulses, active precordium, reduced diuresis, a cardiothoracic index greater than 0.6. Murmurs are often present, as is the need for mechanical ventilation or an increase of the parameters of the ventilator. A total of 3 or more criteria suggests PDA with hemodynamic repercussions.

The echocardiogram was performed in every patient prior to and after treatment with paracetamol, taking into account all data which defines the magnitude of the ductus arteriosus, such as ductal dimensions >1.5 mm, left atrium to aorta ratio (LA/Ao) >1.3 mm, the presence of left to right short-circuits and a ductus arteriosus-aorta ratio >0.5.[11]

Files that showed PDA, but without hemodynamic repercussions or with additional pathologies like congenital cardiopathies, were excluded.

In the included files, a treatment with paracetamol at 15 mg/kg/dose every 6 h for 6 days was documented as a first line of treatment for hemodynamically unstable PDA closure, since access to intravenous medications such as indomethacin or ibuprofen was limited due to importation problems on behalf of the supplier, leaving this as the only alternative for treatment through pharmacological closure with paracetamol and, if this failed, we turned to surgical closure. Additionally, a control echocardiography was documented in every file at the end of the 6-day period.

Patients were divided into two groups for their analytical comparison. The first group was made up of patients who had been successful in the treatment with paracetamol, whereas the second group was made up of patients for whom treatment had failed and required surgery.

Moreover, statistical analysis included more other variables like maternal aspects of prenatal control, clinical characteristics of the newborn, and morbidity and mortality data, such as hyaline membrane disease (HMD), sepsis, bronchopulmonary dysplasia (BPD), intraventricular hemorrhaging (IVH), and retinopathy of prematurity (ROP).

The statistical software SPSS version 20 was used. Non-parametric tests were administered (Chi square) with an alpha value of 0.05, and the null hypothesis was rejected when the critical value was lower than 0.05.

Results

A total of 24 charts reporting hemodynamically unstable PDA treated with paracetamol were obtained during the period from March 1st, 2013 to September 1st, 2014. The effectiveness of the closure of the ductus arteriosus with paracetamol was 83.3% (in 20 patients), finding a significant difference in the measurements of the diameter of the ductus arteriosus before and after the treatment (2.5 [$\pm$0.8] mm vs. 0.8 [$\pm$1.1] mm, $P < 0.001$).

The mothers' ages ranged from 13–38 years, with a maximum of 3 pregnancies. Seven of the mothers (29%) presented some pain during pregnancy, emphasizing urinary tract infections and preeclampsia. Of all mothers, 79% had adequate prenatal care.

Of the population studied, 13 patients were female (54%), and 11 were male (46%). The gestational age between the treatment failure and success groups was not found to be statistically significant (30 vs. 27.5 s) ($P = 0.212$), nor was their weight in grams (1150 g vs. 1.125 g) ($P = 0.510$).

Weight was also classified according to trophism as follows: appropriate for gestational age (AGA), small for gestational age (SGA), and large for gestational age (LGA), without statistical significance. Apgar at 5 min was very similar in both groups, with a minimum score of 4 and a maximum score of 9 points ($P = 0.329$). Regarding neonatal morbidity, it was noted that after failing to respond to paracetamol treatment, neonatal sepsis obtained a significant value ($P = 0.047$), compared to 40% of patients that were successfully treated. In addition, DBP was found in 100% of failures of treatment with paracetamol vs. 25% in successful patients, giving a P value = 0.038 (see Table 1).

As for neonatal mortality, it was documented that 2 patients who had been successful in treatment with paracetamol died 15–20 days after closing the ductus arteriosus.