



Case Report

Successful Closure of Patent Ductus Arteriosus by Late Pharmacologic Treatment in a Small Preterm Infant

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Abstract: The ductus arteriosus (DA) is a temporary communicative pathway that connects the pulmonary artery to the aorta during fetal life. Although usually closing on its own in the initial days of postnatal life, the persistent patency of the DA is common in preterm or low birth weight babies, and can lead to life-threatening complications. Early diagnosis and pharmacologic management of patent ductus arteriosus (PDA) could prevent further need for invasive surgery or transcatheter intervention. Pharmacologic treatment for PDA closure in preterm infants is achieved by cyclooxygenase inhibitors (COXi) and paracetamol. However, their effectiveness is fully demonstrated when they are used early within the first week of postnatal life. We report here the case of a severe preterm infant of 27 weeks gestation age with extremely low birth weight (995g), who had a PDA with moderate to severe shunting closed after late administration of intravenous ibuprofen. Ibuprofen was started on postnatal day 40, and the PDA got closed after a three-day course of treatment. No complication related to the treatment was reported. The DA remained closed when the infant was seen on review for echocardiography at the age of six months. Wherever cardiac surgery and transcatheter intervention are not available nor affordable, possible effectiveness of COXi even in case of late diagnosis of PDA, offers an unexpected opportunity to cure at a very cheaper cost, one of the commonest congenital heart disease.

Keywords: Patent Ductus Arteriosus, Preterm Infant, Ibuprofen

1. Introduction

In term new-born infants, the ductus arteriosus (DA) closes functionally 18 to 24 hours after delivery. In 90% of preterm infants the closure occurs within the first 60 hours of life [1]. Permissibility of the DA beyond 72 hours can lead

to more or less severe clinical events, depending on the significance of the shunting: it could be pulmonary oedema, broncho-pulmonary dysplasia, ventricular haemorrhage, necrotising enterocolitis, or neonatal death [2, 3].

Number of studies proved the effectiveness of non-selective cyclooxygenase inhibitors (COXi) such as indomethacin or

ibuprofen, and more recently that of paracetamol in the closure of hemodynamically significant patent ductus arteriosus (PDA) in preterm new-born [4-12]. COX_i have high effectiveness in ductal closure when they are used very early within the first week of life [13-15]. Cases of PDA closed by pharmacologic treatment after 14 days of life are scarce.

We report here the case of a symptomatic PDA, closed after late administration of intravenous ibuprofen, in the 40th day of life of an extremely low-birth weight (ELBW) preterm infant.

2. Case Presentation

It was a 40 day old baby girl, born after 27 weeks gestation, with Apgar score of 8 then 9. Birth weight was 995g and height was 35cm. History of pregnancy was uneventful; the mother did not report any fever, nor anti-inflammatory drug intake during antenatal period.

The new-born was admitted in the 24th hour of life in the Department of Neonatology of Saint Camille Hospital of Ouagadougou for prematurity and moderate respiratory distress, with a Silverman score of 4. On admission, general condition of the new-born was fair; temperature was 35°C, respiratory rate was 47 cycles per minute, heart rate was 128 beats per minute and oxygen pulse saturation on room air was 93%. Heart and lung auscultation was normal. On laboratory analysis, there was low serum sodium (126 mmol/l); haemoglobin rate was 17.9 g/dl and leucocytes rate was 10 000/mm³ with 55% lymphocytes.

Neonatal sepsis was later diagnosed based on the association of unexplained severe prematurity with respiratory distress, and a high C-reactive protein level (65 mg/l) on day 3 of admission. The new-born received intravenous antibiotic course combining ampicillin at the dose of 50 mg 12 hourly over a period of eight days, and gentamicin at the dose of 2.5 mg 24 hourly over four days. He also got intravenous betamethasone at the dose of 0.125 mg 24 hourly over 72 hours, and caffeine citrate at an initial dose of 20 mg followed by a maintenance dose of 5 mg 24 hourly over three weeks. Daily hydric and electrolyte input was started with 90 ml of intravenous 10% dextrose, 3 ml of 10% calcium gluconate, 2 ml of 10% sodium chloride, regularly adjusted according to weight and age. After a three-week period of improvement, the baby had recurrence of respiratory distress syndrome with cyanosis of extremities, pulse saturation of 89% on room air and cardiac murmur heard in the left sub-clavicular area. Transthoracic echocardiography was performed on day 21 of admission and diagnosed a PDA of 1.6 mm with moderate to severe left to right shunting assessed by the method of Bart Van O and al. [4]. A turbulent diastolic flow was easily detectable at all sites of the pulmonary trunk (figure 1); dilatation of the left atrium was present with a left atrium to aortic root ratio of 1.77 (figure 2). The maximal velocity of the ductal left to right shunt was 3.76 m/sec (figure 3). Systolic function of both ventricles was normal, and systolic pulmonary arterial pressure was normal at 33 mmHg.

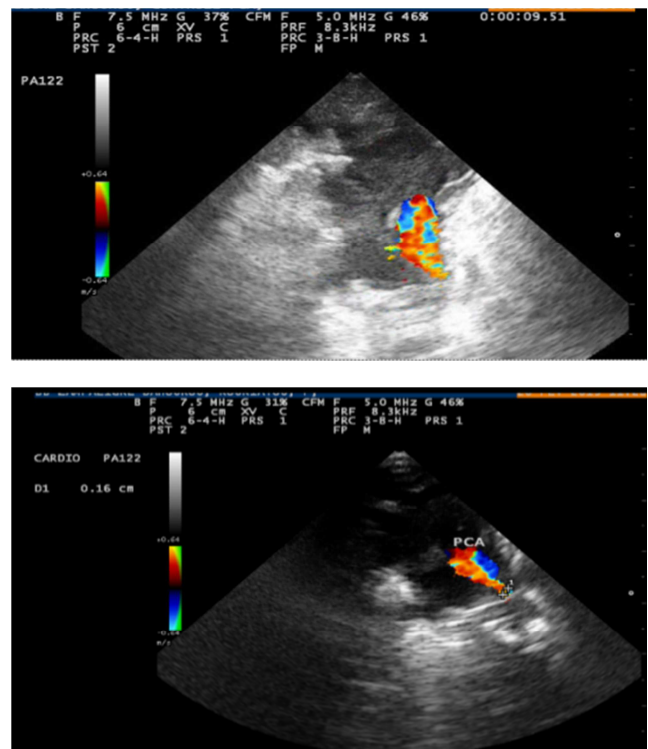


Figure 1. Colour Doppler in parasternal short axis, showing the left to right shunting of PDA in the pulmonary artery trunk.

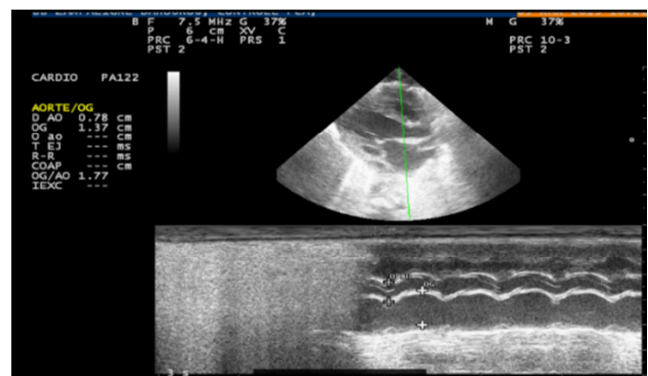


Figure 2. Time-motion mode on parasternal long axis view, showing a dilated left atrium with a left atrium to aortic root ratio of 1.77.

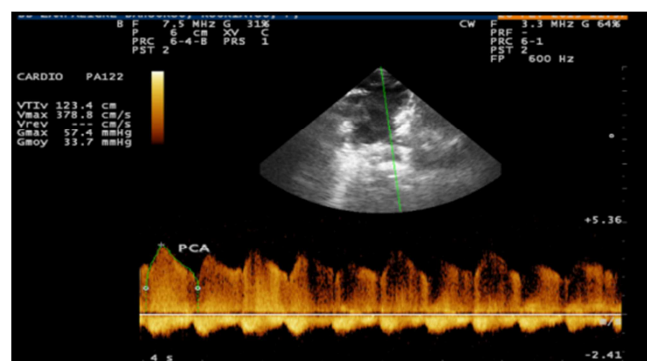


Figure 3. Continuous wave Doppler in parasternal short axis, showing the shunting through the patent ductus arteriosus with a maximal flow velocity of 3.78 m/sec and maximal gradient of 57 mmHg.

Before this clinical presentation, continuous nasal oxygen

(0.5l/min) and oral furosemide at the dose of 3 mg once daily were administered to the baby. A pharmacologic closure of the PDA was attempted with intravenous paracetamol at the dose of 15 mg/kg 6 hourly over three days. Echocardiography was repeated 24 hours after paracetamol course but revealed a failure of PDA closure, with persistence of severe shunting through the ductus. Treatment with furosemide was maintained, but oxygen was given intermittently in accordance with the level of desaturation and the episodes of acute dyspnoea.

Despite the late delay, we advised another attempt of pharmacologic closure, using this time intravenous ibuprofen. The infant's parents were warned on the poor chances of treatment success, but gave their consent. The injectable ibuprofen was ordered from the Republic of South Africa; it wasn't available in the West African sub-region. When we finally got the ibuprofen, treatment was started at day 40 of postnatal life at the dose of 10 mg/kg followed by 5 mg/kg after 24 hours and 5 mg/kg again after another 24 hours. Infant was weighing 1265g by then.

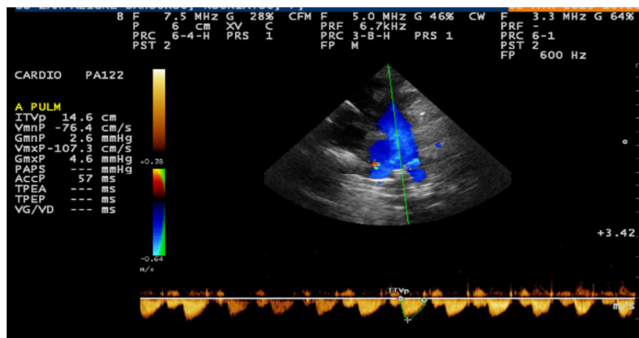


Figure 4. Check echocardiography 24 hours after ibuprofen course, showing the absence of shunting through the ductus arteriosus.

A check echocardiography performed 24 hours after treatment did no more visualize a shunting through the DA, meaning thus a successful closure of the PDA by the ibuprofen (figure 4 and 5).

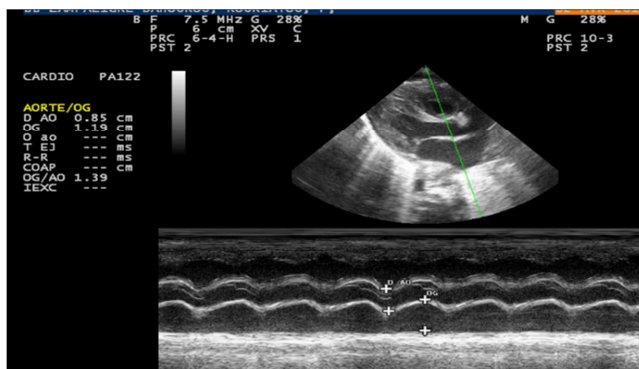


Figure 5. Check echocardiography one month later showing a normalized size of left atrium (left atrium to aortic root ratio of 1.39).

No complications like renal failure nor gastro-intestinal bleedings secondary to the treatment were reported. Serum creatinine was 77 $\mu\text{mol/l}$. Cranial ultrasound scan performed after ibuprofen course found bilateral chronic sub-ependymal

haemorrhage (8 mm x 5 mm on right side and 8 mm x 4 mm on left side), with no clinical manifestations. That chronic haemorrhage was probably not linked to the treatment, but due to the severe preterm condition of the infant.

The clinical outcome was good; dyspnoea totally regressed, furosemide treatment was discontinued and infant weaned on oxygen. She was discharged from hospital on postnatal day 53 with a weight of 1470g. A follow up echocardiography performed at the age of six months did not show a re-opening of the PDA.

3. Discussion

55% of ELBW (< 1000 g) infants have been described to have a symptomatic PDA that ultimately leads to pharmacological treatment, like that of the case we've reported [18, 19]. Spontaneous closure of the DA occurs two to six days after birth in about 34% of ELBW neonates and within the first year of life in the majority of very low birth weight neonates (< 1500 g) [18, 20]. Even so, 60 to 70% of preterm neonates below 28 weeks gestation receive pharmacologic or surgical therapy of PDA, usually with the intention to prevent from the complications described earlier [21, 22]. To date it is not clearly established when exactly, and which of the conservative pharmacologic treatment or the surgical approach are the most beneficial. The effectiveness of COX_i and paracetamol in the closure of PDA depends on gestational age. These drugs are less effective in severely preterm neonates, a fact often attributed to inadequate contraction of the immature DA smooth muscle cell, and mostly to the failure of intimal cushion formation [23-26]. Moreover effectiveness of COX_i is fully demonstrated only when they are given early, usually within the first week of postnatal life [13-15]. In advanced postnatal age, the decreased effectiveness of COX_i could be related to the poor role of prostaglandins E₂ in the permissibility of the DA [27, 28].

Most of pharmacologic treatments reported in the literature were given before the 14th day of postnatal life [13-15, 29-36]. According to Chuan-Zhong Yang in China, the rate of ductal closure after indomethacin therapy dropped from 85% in the first 24 hours of life to only 48% when the treatment was started at the 72nd hour [28]. H Popat and al. in their trial using indomethacin, reported failure of PDA closure when treatment was started after 28 days of life [37]. Achanti and al., like Pacifici, focused on the inefficiency of indomethacin administered after the 8th week postnatal [27, 38].

However, some authors reported few cases of PDA closure after late pharmacologic treatment. Amitoj Shing China notified in 2016 a case of PDA closure after late administration of paracetamol at 4 weeks of life in a very low birth weight preterm infant, whereas in our report, paracetamol started on postnatal day 21 failed to close the PDA [39]. The same author reported earlier in 2014 a case of PDA closure after very late administration of indomethacin on postnatal day 52 [40]. That infant was an ELBW preterm in whom several attempts of pharmacologic closure with either

ibuprofen or indomethacin started since postnatal day 10 initially failed, with alternations of closure and re-opening. Hammerman and al. reported a case of late closure of PDA with paracetamol treatment on 35th day of postnatal life, whereas two previous attempts with ibuprofen on day 6 then day 10 failed [41]. Sterniste and al. in 1998 reported the latest delay of PDA closure at the 11th week of postnatal life, with indomethacin in an ELBW preterm infant [42].

4. Conclusion

Various cases in the literature prove that pharmacologic closure of PDA in preterm infants is sometimes effective at an advanced postnatal age. We've achieved a successful closure of PDA after late administration of intravenous ibuprofen in a 40 day old baby with ELBW. The use of ibuprofen has proved safe, with no complications reported. Therefore, it should be tried on first intention in similar cases, in view of the risks linked to surgical ligation and the technical challenges of catheterization in infants weighing less than 6 kg [43]. In the absence of contra indications, medication courses can be repeated even if the first protocols fail to close the PDA.

Moreover, the lack of technical facilities for surgical ligation or percutaneous occlusion of PDA in some areas, and prohibitive cost of these methods should strongly enhance the systematic use of pharmacologic treatments even in case of advanced postnatal age.

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