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

(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 COXi 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 COXi 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 COXi could be related to the poor role of prostaglandins E_2 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.

References

- [1] N. Evans and L. N. Archer. Post Natal Circulatory Adaptation in Healthy Term and Preterm Neonates. *Arch Dis Child*. 1990; 65: 24-6.
- [2] R.B. Cotton, M. T. Stahlman, H. W. Bender, and al. Randomized Trial of Early Closure of Symptomatic Patent Ductus Arteriosus in Small Preterm Infants. *J Pediatr*. 1978; 93: 647-51.
- [3] M. V. Speziale, R. G. Allen, C. R. Henderson, and al. Effects of Ibuprofen and Indomethacin on Regional Circulation in Newborn Piglets. *Biol Neonate* 1999; 76: 242-52.
- [4] B. V. Overmeire, K. Smets, D. Lecoutere, and al. A Comparison of Ibuprofen and Indomethacin for Closure of Patent Ductus Arteriosus. *N Engl J Med*. 2000; 343: 674-81.
- [5] A. Ohlsson and P. S. Shah. Paracetamol (acetaminophen) for Patent Ductus Arteriosus in Preterm or Low Birth Weight Infants. *Cochrane Database Syst Rev*. 2018; 4: CD010061.
- [6] R. I. Clyman. Medical Treatment of Patent Ductus Arteriosus in Premature Infants. In: *Long WA, ed. Fetal and Neonatal Cardiology*. Philadelphia: WB Saunders, 1990: 682-90.
- [7] R. I. Clyman. Recommendations for the Postnatal Use of Indomethacin: An Analysis of Four Separate Treatment Strategies. *J Pediatr*. 1996; 128: 601-7.
- [8] A. Varvarigou, C. L. Bardin, K. Beharry, and al. Early ibuprofen Administration to Prevent Patent Ductus Arteriosus in Premature Newborn Infants. *JAMA* 1996; 275: 539-44.
- [9] M. A. Heymann, M. A. Rudolph, and N. H. Silverman. Closure of the Ductus Arteriosus in Premature Infants by Inhibition of Prostaglandin Synthesis. *N Engl J Med*. 1976; 295: 530-3.
- [10] W. F. Friedman, M. J. Hirschklau, M. P. Printz, and al. Pharmacologic Closure of the Patent Ductus Arteriosus in Premature Infant. *N Engl J Med*. 1976; 343: 526-9.
- [11] T. F. Yeh, J. A. Luken, A. Thalji, and al. Intravenous Indomethacin Therapy in Premature Infants with Persistent Ductus Arteriosus – a Double Blind Controlled Study. *J Pediatr*. 1981; 98: 137-45.
- [12] J. Neu, R. L. Ariagno, J. B. Johnson, and al. A double Blind Study of the Effects of Oral Indomethacin in Preterm Infants with Patent Ductus Arteriosus who Failed Medical Management. *Pediatr Pharmacol*. 1981; 1: 245-9.
- [13] V. Gournay. Management of Patent Ductus Arteriosus in Preterm Infants: An Evidence-Based Approach. *Arch Pédiatr*. 2017; 24 (2): 175-79.
- [14] A. Ohlsson, R. Walia, and S. S. Shah. Ibuprofen for the Treatment of Patent Ductus Arteriosus in Preterm or Low Birth Weight (or both) Infants. *Cochrane Database Syst Rev*. 2015; 2: CD003481.
- [15] J. Lee, V. S. Rajdurai, K. W. Tan, and al. Randomized Trial Prolonged Low-Dose versus Conventional-Dose Indomethacin for Treating Patent Ductus Arteriosus in Very Low Birth Weight Infants. *Pediatrics* 2003; 112: 345-350.
- [16] M. V. Betkerur, T. F. Yeh, K. Miller, and al. Indomethacin and its Effects on Renal Function and Urinary Kallikrein Excretion in Premature Infants with Patent Ductus Arteriosus. *Pediatrics* 1981; 68: 99-102.
- [17] J. M. Rennie, J. Doyle, and R. W. Cooke. Early Administration of Indomethacin to Preterm Infants. *Arch Dis Child* 1986; 61: 233-8.
- [18] J. Koch, G. Hensley, L. Roy, and al. Prevalence of Spontaneous Closure of the Ductus Arteriosus in Neonates at a Birth Weight of 1000 gram or Less. *Pediatrics* 2006; 117 (4): 1113-21.
- [19] J. Richards, A. Johnson, G. Fox, and M. Campbell. A Second Course of Ibuprofen is Effective in the Closure of a Clinically Significant PDA in ELBW infants. *Pediatrics* 2009; 124 (2).
- [20] K. Herrman, C. Bose, K. Lewis, and M. Laughon. Spontaneous Closure of the Patent Ductus Arteriosus in Very Low Birth Weight Infants Following Discharge from the Neonatal Unit. *Arch Dis Child Fetal Neonatal Ed*. 2009; 94 (1): 48-50.
- [21] R. I. Clyman. Ibuprofen and Patent Ductus Arteriosus. *N Engl J Med*. 2000; 343 (10): 728-30.
- [22] E. G. Shannon, H. Hamrick, and H. Georg. Patent Ductus Arteriosus of the Preterm Infant. *Pediatrics* 2010; 125: 1020 – 30.
- [23] C. A. Mason, J. L. Bigras, S. B. O'Blenes, and al. Gene Transfer in Utero Biologically Engineers a Patent Ductus Arteriosus in Lambs by Arresting Fibronectin-Dependent Neointimal Formation. *Nat Med*. 1999; 5 (2): 176-82.
- [24] C. A. Mason, P. Chang, C. Fallery, and M. Rabinovitch. Nitric Oxide Mediates LC-3-Dependent Regulation of Fibronectin in Ductus Arteriosus Intimal Cushion Formation. *FASEB J*. 1999; 13 (11): 1423-34.

- [25] U. Yokoyama, S. Minamisawa, H. Quan, and al. Chronic Activation of the Prostaglandin Receptor EP4 Promotes Hyaluronan-Mediated Neointimal Formation in the Ductus Arteriosus. *J Clin Invest*. 2006; 116 (11): 3026–34.
- [26] K. N. Ivey and D. Srivastava. The Paradoxical Patent Ductus Arteriosus. *J Clin Invest*. 2006; 116 (11): 2863–65.
- [27] B. Achanti, T. F. Yeh, and R. S. Pildes. Indomethacin Therapy in Infants with Advanced Postnatal Age and Patent Ductus Arteriosus. *Clin Invest Med*. 1986; 9 (4): 250–53.
- [28] C. Z. Yang and J. Lee. Factors Affecting Successful Closure of Hemodynamically Significant Patent Ductus Arteriosus with Indomethacin in Extremely Low Birth Weight Infants. *World J Pediatr*. 2008; 4 (2): 91–96.
- [29] L. Cooke, P. A. Steer, and P. G. Woodgate. Indomethacin for Asymptomatic Patent Ductus Arteriosus in Preterm Infants. *Cochrane Database Syst Rev*. 2003; 1: CD003745.
- [30] B. K. David. The Treatment of Patent Ductus Arteriosus in Preterm Infants. A Review and Overview of Randomized Trials. *Semin Neonatol*. 2001; 6: 63–73.
- [31] B. Van Overmeire, P. Vanhaesebrouck, and J. P. Langhendries. Early versus Late Selective Treatment of Patent Ductus Arteriosus in Preterm Infants with Respiratory Distress Syndrome. *Ped Res*. 1998; 43 (suppl 2): 200.
- [32] K. M. Weesner, R. G. Dillard, R. J. Boyle, and S. M. Block. Prophylactic Treatment of Asymptomatic Patent Ductus Arteriosus in Premature Infants with Respiratory Distress Syndrome. *Southern Med J*. 1987; 80: 706–708.
- [33] H. Babaei, R. Nemati, and H. Daryoshi. Closure of Patent Ductus Arteriosus with Oral Acetaminophen in Preterm Neonates: a Randomized Trial. *Biomedical Research and therapy* 2018; 5 (2): 2034-44.
- [34] N. M. Bagheri, P. Niknafs, F. Sabsevari, and al. Comparison of Oral Acetaminophen versus Ibuprofen in Premature Infants with Patent Ductus Arteriosus. *Iran J Pediatr*. 2016; 26 (4): e3975.
- [35] A. E. El-Mashad, H. El-Mahdy, D. El Amrousy, and M. Elgendy. Comparative Study of the Efficacy and Safety of Paracetamol, Ibuprofen, and Indomethacin in Closure of Patent Ductus Arteriosus in Preterm Neonates. *Eur J Pediatr*. 2017; 176 (2): 233-40.
- [36] M. Gillam-Krakauer and J. Reese. Diagnosis and Management of Patent Ductus Arteriosus. *Neoreviews* 2018; 19 (7): 394-402.
- [37] H. Popat, V. Kapoor, and J. Travadi. Patent Ductus Arteriosus in Infants < 29 Weeks Gestation – Outcomes and Factors Affecting Closure. *Indian Pediatrics* 2011; 49 (8): 615-20.
- [38] G. M. Pacifici. Clinical Pharmacology of Indomethacin in Preterm Infants: Implications in Patent Ductus Arteriosus Closure. *Paediatr Drugs* 2013; 15: 363–76.
- [39] A. S. Chhina and A. Shenoi. Paracetamol-Responsive Patent Ductus Arteriosus in a Late Preterm Very Low Birth Weight Neonate at 4 Weeks Postnatal Age. *Muller J Med Sci Res*. 2016; 7: 131-2.
- [40] A. S. Chhina, B. Kumar Sharma, M. Raja, and al. Indomethacin-Responsive Patent Ductus Arteriosus in an Extremely Preterm Infant at 8 Weeks Postnatal Age. *Indian J Pediatr*. 2015; 82: 655-56.
- [41] C. Hammerman, A. Bin-Nun, E. Markovitch, and al. Ductal Closure with Paracetamol: A Surprising New Approach to Patent Ductus Arteriosus Treatment. *Pediatrics* 2011; 128: 1618–21.
- [42] W. Sterniste, C. Gabriel, and M. Sacher. Successful Closure of the Patent Ductus Arteriosus by Indomethacin in an Extremely Low Birth Weight Infant of Very Advanced Postnatal Age. *Pediatr Cardiol*. 1998; 19: 256–8.
- [43] A. E. Baruteau, S. Hascoët, J. Baruteau, and al. Transcatheter Closure of Patent Ductus Arteriosus: Past, Present and Future. *Arch Cardiovasc Dis*. 2014; 107: 122-32.