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Use of rectal ibuprofen for PDA closure in preterm neonates

D. Surkov, A. Obolonskiy, O. Kapustina, D. Volkov

NICU, Regional Children's Hospital, Dnepropetrovsk, Ukraine

Corresponding author: D. Surkov, NICU, Regional Children's Hospital, Kosmitcheskaya St. 13, 49100 Dnipropetrovsk, Ukraine. Email: densurkov@hotmail.com

Key points

Closure of hemodynamically significant patent ductus arteriosus is one of the most important questions in neonatal intensive care, especially for preterm babies. COX inhibitors are routinely used present time. Ibuprofen and indomethacin show the equal efficacy and less adverse events using ibuprofen. A high cost of intravenous ibuprofen leads to searching for alternative ways of administration with comparable efficacy. A rectal administration of ibuprofen might be a cheap, effective and safe method for PDA closure in preterm neonates.

Abstract

Objective

To evaluate efficacy and safety of rectal form of ibuprofen and comparing to indomethacin for treatment of patent ductus arteriosus (PDA) in premature neonates.

Methods

Single-center, cohort, prospective study without pre-randomization was performed in 38 preterm infants at gestational age 25-31 weeks were treated in NICU of Dnepropetrovsk Regional Children's Hospital (Ukraine) during 2010-2012. At admission PDA diameter, direction of shunt and hemodynamic significance of the duct were determined in premature neonate using ultrasound (US) and Doppler. All patients received restrictive infusion therapy and dobutamine intravenously. Cyclooxygenase (COX) inhibitors were administered for 3 days; if ultrasound examination verified hemodynamically significant PDA (HSPDA), the treatment was continued until PDA closure but not longer than 14 days. Children of the 1st group (n=20) received oral indomethacin during 3 days; in case of gut paresis treatment was continued by i.v. or rectal ibuprofen. Patients of the 2nd group (n=10) were prescribed oral indomethacin only and in 3rd group (n=8) only ibuprofen was used in rectal form.

Results

In patients received rectal form of ibuprofen PDA was completely closed on the average two times faster (the difference is significant, $p<0.05$). In patients of all three groups, conservative therapy was effective: no need for surgical treatment (duct clipping) appeared. None of the patients developed necrotic enterocolitis (NEC) stage 3 and intraventricular hemorrhage (IVH) grades 3-4. The choice of COX inhibitors had no influence on the severity of bronchopulmonary dysplasia. No mortality occurred in all groups of patients.

Conclusions

The use of rectal ibuprofen is a cheap, effective and safe method for PDA closure and might be an alternative to intravenous way of administration. Rectal and parenteral forms of ibuprofen demonstrated similar effectiveness in treatment of the PDA. As far as the COX inhibitors were studied in small groups of patients, this research should be continued.

Keywords: patent ductus arteriosus; cyclooxygenase

inhibitors; ibuprofen; premature neonates.

Introduction

Therapy for PDA closure is one of the corn stones in state of the art neonatology. Nevertheless, such questions as "What is a treatment of choice?", "When to start closing?", "When surgical procedure becomes necessary?" are still unclear. The most complete comparative analysis of this data is represented by D.B. Knight (2001) [9]. Recommendations for management of PDA in preterm infants significantly vary in different countries and hospitals. One of the most promising protocols for PDA treatment was published by N. Evans (2005) [4]. The Guidelines of the Department of Neonatal Medicine, Royal Prince Alfred Hospital recommend usage of non-steroidal anti-inflammatory drugs (NSAIDs) under the control of diameter of PDA which can been changed in time. Echocardiography should be performed in all at-risk babies (RDS or no antenatal steroidal prophylaxis) at the age of 3-6 hours after birth. If the diameter of the duct is over the median 2.0 mm at the age of 3 hours after birth infant will receive the first administration of the COX inhibitor [4].Traditionally such non-steroidal anti-inflammatory drugs as indomethacin and ibuprofen are used as COX inhibitors. Recently the possibility of acetaminophen administration for PDA closing is discussed [5, 12]. Indomethacin and ibuprofen are both sufficiently effective for PDA closure but simultaneously these drugs have potentially dangerous complications including oliguria, hyponatremia, gastrointestinal bleeding, transient decreasing of renal, mesenteric and brain blood flow. Described above adverse events have been initially studied for indomethacin. The use of ibuprofen for PDA closing was proposed as alternative to indomethacin. Ibuprofen has less influence on the renal, cerebral and mesenteric circulation [13, 15, 18]. In comparative randomized study by Van Overmeire (2005) 142 infants (GA 24-32 weeks) with RDS and hemodynamically significant (HS) PDA were involved. All the neonates received either indomethacin or ibuprofen. Both drugs were effective in PDA closing. There was no difference in the frequency of re-treatment and surgery. Lower incidence of oliguria was registered in infants received ibuprofen [18]. A meta-analysis of 16 studies (876 VLBW neonates, ibuprofen or indomethacin for treatment of PDA) showed no significant difference in the incidences of treatment failure, need in surgical procedures and mortality. Also there was no reliable difference in development of bronchopulmonary dysplasia (BPD), severe intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), NEC with bowel perforation, retinopathy of prematurity (ROP) [11]. In six studies (336 babies) there were found significantly lower levels of serum creatinine and in 3 studies (358 neonates) there was lower rate of incidences of oliguria in infants receiving ibuprofen [1, 2]. The expensive price for intravenous ibuprofen comparing to indomethacin, the inaccessibility of this drug form in limited resource countries resulted in studying of safety and efficacy of enteral forms of ibuprofen for PDA closure. Currently 7 small randomized studies were conducted to resolve this issue (total number of newborns n=208) [3]. However, several publications reported about serious complications associated with enteral use of ibuprofen, the development of acute renal failure and bowel perforation which do not let to use this method for PDA treatment routinely [10, 17, 19]. One of the controversial issues in the management of neonates with HSPDA remains the possibility and expedience of ibuprofen administration rectally. Diagnostic value of measurement of the diameter of the PDA and direction of shunting is beyond any doubt. Other signs of hemodynamic significance of PDA are still widely discussing in many articles [6, 14, 16]. One of the main criteria for hemodynamic significance of PDA is diastolic flow in postductal part of descending aorta. In the presence of left-to-right shunting blood flow during diastole goes through the duct and «null» or retrograde diastolic flow is registered by Doppler. Besides

hemodynamic significance of shunting of blood through PDA also the ratio of the left atrium diameter to the aortic root diameter (LA / Ao), the ratio of end-diastolic size of the left ventricle to the aortic root, and rise of the indices of vascular resistance in the cerebral vessels (Resistance Index, RI) are used to verify the diagnosis. [6,7,14] According to some authors in infants with PDA the retrograde flow in post ductal part of descending aorta has reliable coupling with fluctuation of cerebral blood flow and reduction in end-diastolic and mean blood flow velocity [6-8, 14, 20].

Methods

Single-center, cohort, prospective study without pre-randomization was performed in 38 preterm infants at gestational age 25-31 weeks were treated in NICU of Dnepropetrovsk Regional Children's Hospital (Ukraine) during 2010-2012.

Inclusion criteria: gestational age 25 to 31 weeks, RDS, HSPDA. Exclusion criteria: IVH grade III-IV, congenital malformations, early onset neonatal sepsis. Babies were admitted to NICU at the age of 2 DOL on the average. Routinely PDA was checked during first 24 hours by echocardiography and Doppler via transthoracic access; ultrasound evaluation of the PDA was performed daily including diameter of the duct, the direction of shunting and hemodynamic significance using Doppler patterns of cerebral blood flow in anterior cerebral artery. According to several studies [1, 2, 16] there is a correlation between the characteristics of blood flow in the descending aorta and cerebral vessels in neonates. Therefore, considering the high risk of neonatal IVH and a special emphasis on the brain protection, in addition the traditional ultrasound signs of hemodynamic significance of PDA we assessed by the blood flow patterns in the anterior cerebral artery (ACA). Special attention was paid to the restrictive type of blood flow (RI ≥0.80) and the emerging of retrograde diastolic blood flow. Treatment protocol included: first three days oral indomethacin was applied dosing 0.2-0.1-0.1 mg/kg/day. In case of symptoms of the bowel paresis oral indomethacin was canceled and three-day course of i.v. ibuprofen was prescribed in dose of 10-5-5 mg/ kg/day. At the end rectally ibuprofen should be given dosing 20-10-10 mg/kg/day. In event of first 3-day course of COX inhibitors insufficiency we continued by second course of same dosing until closing the PDA but not more than 14 days. The current guideline recommends surgical clipping of PDA if COX inhibitor therapy fails after 14 days. All infants received restrictive fluid intake (40-50 ml/kg/day) and dobutamine inotropic support at dose of 7.5-10 µg/kg/min. depending on ACA cerebral blood flow. All the patients retrospectively were divided into three groups as following: babies of the first group (n = 20) received indomethacin orally and subsequently ibuprofen i.v. because of PDA presence. Infants of the second group (n = 10) successfully received just oral indomethacin 0.2-0.1-0.1 mg/kg/day up to PDA closure been confirmed but not more than 14 days. In the third group (n=8) a three-day course of rectal ibuprofen in dose of 20-10-10 mg/kg/day has been administered as a starting therapy. In case of PDA shunting at the end of 3rd day rectal ibuprofen was continued in dose of 10 mg/kg/day until the PDA was closed. Baseline characteristics of all groups are presented in Table 1. There was no significant diversity in gestational age, weight or time of admission to NICU between these groups.

Results and discussion

The summary results of the PDA treatment are presented in Table 2. As we can see from table 2 in group 3 patients received ibuprofen rectally showed complete PDA closing two times faster comparing with other groups (the diversity is significant; $p<0.05$). In all three groups conservative treatment was effective and we had no reasons to use surgery (duct clipping). No baby among all the patients revealed NEC grade III; NEC grade II (M.G. Bell et al, 1978) was observed in 2 patients of group 1 and in one patient of group 2. No one among premature neonates included in this study had IVH grade III-IV; IVH grade II was registered in 6 infants from first group, in 3 cases – from second group and in 2 – in group 3. BPD was developed in 50% cases of all groups (p=0.13) therefore we can conclude that choice of COX inhibitor didn't influence the BPD morbidity in our study. There were no deaths in all groups.

Characteristics (M±m) (min-max)	Indomethacin + Ibuprofen (n=20)	Indomethacin p.o. (n=10)	Ibuprofen per rectum (n=8)
Gestational age, weeks	28.5±1.08 (26-31)	28.0±1.03 (27-31)	26.5±1.52 (26-29)
Weight at birth, grams	1210±307.7 (600-1800)	1030±300.7 (700-1600)	1020±352.2 (840-1300)
Diameter of ductus arteriosus, mm	3.0±1.2 (2.2-5.0)	3.0±2.02 (3.0-5.3)	2.8±1.22 (2.0-3.5)

Table 1. Characteristics of the Neonates at Baseline (n=38)

Outcome (M±m) (min-max)	Indomethacin + Ibuprofen (n=20)	Indomethacin p.o. (n=10)	Ibuprofen per rectum (n=8)
PDA closure, DOL	6.0±0.39 (4-7)	4.0±3.89 (4-14)	3.0±0* (3-3)
Duration of MV (days)	7.0±3.05 (1-68)	7.0±1.26 (3-11)	5.5±1.02 (4-8)
Duration of NIV (days)	14.0±3.56 (1-30)	12.0±2.68 (5-26)	10.5±2.58 (2-19)
Inotropes (days)	6.5±2.02 (3-10)	7.0±1.22 (4-10)	4.5±1.56 (3-6)
Feeding starts (day)	12.0±2.23 (4-25)	11±2.56 (7-17)	11.0±2.68 (5-14)
*The diversity of parameters in groups 1 and 3 is significant ($p<0.05$)			

Table 2. Outcomes of Treatment for PDA by Different COX Inhibitors in Premature Neonates.

Conclusions

1. Using of rectal form of ibuprofen is cheap, effective and safe method for PDA closing and it should be used as an alternative to ibuprofen intravenous administration.
2. Rectal and intravenous administrations of ibuprofen show similar efficacy in the PDA closure in preterm neonates.
3. Comparing to i.v. ibuprofen or oral indomethacin rectal ibuprofen shows less adverse events.
4. As far as study of efficacy and safety of rectal ibuprofen was conducted in small samples it needs to be continued.

List of abbreviations

BPD - bronchopulmonary dysplasia

COX - cyclooxygenase

DOL – day of life

ELBW - extremely low birth weight

GA - gestational age

HSPDA - hemodynamically significant patent ductus arteriosus

IVH - intraventricular hemorrhage

MV - mechanical ventilation

NEC - necrotizing enterocolitis

NICU – neonatal intensive care unit

NIV - non-invasive ventilation

NSAIDs - non-steroidal anti-inflammatory drugs

PDA - patent ductus arteriosus

PVL - periventricular leukomalacia

RDS - respiratory distress syndrome

RI - Resistant Index, an index of resistance

VLBW - very low body weight

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