The Comparison Between Intravenous *Acetaminophen* Versus Oral *Ibuprofen* in Preterm Newborns With Patent Ductus Arteriosus: A Clinical Trial

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Abstract- Oral ibuprofen has been known as a conventional treatment for closing patent ductus arteriosus (PDA) in preterm newborns. Since the use of it might lead to various side effects, other treatments needed to be evaluated. Therefore in a prospective study, we compared the efficacy and safety of intravenous acetaminophen versus oral ibuprofen for the closure of PDA. In this study which was done prospectively and under control, 50 preterm neonates with gestational ages and weights less than 37 weeks old and 2500 grams, respectively, who had PDA, large enough hemodynamically, were included in the study. The patients were divided into two groups: A (intravenous acetaminophen) & B (oral ibuprofen). The two groups were given at most two 3-day courses of the medication (the second course if necessary) and evaluated at the end of each course by echocardiography so as to determine the response to the treatment at each step. The rate of ductal closure, the need for additional treatment, side effects, complications and the newborn's clinical status were recorded. The rate of ductal closure in the both groups after one course of treatment was similar and showed no meaningful significance statistically (P=0.306). But that of the side effects was much higher in group B with a P=0.021. Intravenous Acetaminophen is not only as efficacious as oral Ibuprofen for the treatment of PDA in preterm infants, but also is less likely to lead to side effects and complications.

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Keywords: Patent ductus arteriosus; Acetaminophen; Preterm infants

Introduction

Ductus arteriosus (PDA) remains a frequent problem in premature infants with the respiratory distress syndrome (1). In a large network of neonatal intensive care units, the frequency of patent ductus arteriosus in infants weighing 501 to 1500 g was 31 percent (2) Persistent PDA in preterm infants can lead to serious clinical consequences, and it is one of the main factors affecting the survival rate of premature children and sequalae incidence (3). Hemodynamically significant PDA causes persistent left to right shunting leading to variable blood flow in different organs including brain, kidney, intestine and lungs. Besides these, several neonatal morbidities like bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), and pulmonary hemorrhge/edema have been associated with a persistent PDA leading to increased mortality (4).

Making a bridge between the main pulmonary artery and the descending aorta, the ductus arteriosus (DA) takes the right ventricular output away from the lungs and toward the placenta in the fetus. Within the first three days of life, the presence of a patent ductus arteriosus (PDA) is considered physiologically normal in healthy term and preterm newborn infants (5). The incidence of PDA in term infants is around 57 in 100,000 live births (6), whereas that of preterm infants is expected to be one out of three having a birth weight (BW) of 501 to 1500 g (very low birth weight "VLBW") (7). Furthermore, about half of infants who weigh <1000 g (extremely low birth weight "ELBW") are expected to have a symptomatic PDA that finally needs medical treatment (8). Despite the fact that in around 34% of ELBW neonates and the majority of VLBW neonates, DA closes spontaneously 2 to 6 days postnatally (9) and

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within the first year of life (10), respectively, about 60 to 70% of preterm infants of less than 28 weeks' gestation receive medical or surgical therapy for a PDA (11).

The mechanisms underlying physiologic closure of the DA have been clarified. The medial layer of the DA is made up of smooth muscle fibers which are arranged longitudinally and spirally within a matrix of elastic tissue. Fetal patency is regulated by low oxygen tension and prostanoids, predominantly prostaglandin E2 (PGE2) and prostacyclin (PGI2). PGE2 and PGI1 levels are high in the fetus because of both placental production and diminished clearance by the fetal lungs (12). After birth at term, a postnatal increase in Pa02 and a decrease in circulating vasodilators such as PGE2 and PGI2 will induce constriction of DA smooth muscle cells and consequently functional closure of the ductus in newborns (13). Oxygen regulated mechanisms within the smooth muscle cells of the ductus arteriosus lead to depolarization, which let calcium influx and contraction. On the other hand, potassium channels allow for voltage-gated calcium channels to open and increase calcium influx (14). Immaturity of both these channels leads to decreased effectiveness of oxygen mediated constriction in the preterm rabbit DA (15). Besides, a persistent myosin light-chain phosphorylation is derived from Rho/Rho-kinase pathways which in turn induce calcium sensitization and a permanent vasoconstriction (16). The generation of mitochondrial derived reactive oxygen species seems to be insufficient in the preterm DA (17). Although the role of endothelin-1 as a potent oxygen derived vasoconstrictor in closing the DA is controversial, postnatally, but it seems the effect is executed through G-protein coupling (18).

In preterm infants, the sensitivity for oxygen is reduced, but in addition, the sensitivity to PGE2, nitric oxide (NO), and perhaps endothelin-1 is increased (19). Acting through G-protein coupled receptors, PGE2 activates adenyl cyclase which leads to the production of cyclic adenosine monophosphate (cAMP) so as to relaxe the vascular smooth muscle layers. cAMP concentrations also depend on phosphodiestrase-mediated degradation. Likewise, NO activates guanyl cyclase to produce cyclic guanosine monophosphate (cGMP), which is degraded by a different phosphodiestrase isoform (20). In summary, the mechanisms underlying functional DA closure depend on gestational maturity.

The presence of left to right shunts for instance due to PDA and especially in the setting of preterm respiratory distress with low plasma oncotic pressure and increased capillary permeability, might lead to pulmonary edema, decreased lung compliance and prolonged ventilation with potentially high oxygen load, and probably to BPD/CLD (21). Lung injury accompanied by myocardial dysfunction due to left sided volume overload make preterm infants, born at <1500 g, susceptable to hypoperfusion of vital organs and resultant additional co-morbidities such as IVH, periventricular leukomalacia, NEC, and pre-renal failure (22).

Echocardiographically, the presence of left atrium to Aorta ratio more than 1.4, PDA diameter more than 1.4 and holodiastolic flow reversal in the descending aorta indicate a significant PDA shunt (23). Pulse-wave Doppler of the main pulmonary artery demonstrates a high antegrade diastolic flow (> or equal to 0.5 m/s) (24) A resistance index of > or equal to 0.9 of the anterior cerebral artery is considered as a sign of significant ductal shunting with adverse steal effect (25).

Non-selective cyclooxygenase inhibitors such as indomethacin and ibuprofen, competing with the arachidonic acid substrate for the active cyclooxygenase site, have been recorded to be successful in ductal closure in 70% of cases. Some side effects including gastrointestinal and renal dysfunctions, increased bilirubin level and disturbed platelet aggregation have been recognised following the consumption of these two drugs (26).

For a long time, surgical ligation was the only modification in patients for whom the non-steroidal anti-inflammatory drugs (NSAIDS) were contraindicated (27). Because of the potential complications of an invasive intervention such as surgical ligation, another medication needed to used, so paracetamol (acetominophen) has gained attention as an alternative drug for PDA closure (28). Acting at the peroxidase part, acetaminophen also inhibits prostaglandin synthetase activity of the enzyme (29). Acetaminophen has been tried as an alternative medication for closing PDA because of having less side effects and comparable effectiveness (30).

The aim of this work was to compare the efficacy and side effects of intravenous acetaminophen and oral ibuprofen in the closure of hemodynamically significant PDA in preterm neonates

Materials and Methods

We conducted a controlled clinical trial in the neonatal intensive care unit (NICU) of Imam Khomeini Hospital Complex from Feb 2017 to Feb 2018. In this trial, 50 preterm neonates who had hemodynamically

significant (hs) PDA and who also had a birth weight <2500 g and a gestational age <37 weeks were included. The diagnosis of the newborns who had hs PDA was made echocardiographically. The echocardiographic criteria for the diagnosis of hs PDA in our study were a duct size> 1.5 mm, a left atrium to aortic root ratio >1.5, the end-diastolic reversal of the blood flow in the aorta, and heart failure not explained by any other reason other than the PDA. Those newborns who had persistent pulmonary hypertension of the newborn, life-threatening infection, syndromic manifestations, cyanotic, duct dependent, and any type of complex heart disease were excluded from the study. Our patients were divided into two groups: A (intravenous Acetaminophen) and B (oral ibuprofen). When there was any contraindication for giving ibuprofen such as grade 3-4 IVH, urine output <1 ml/kg/hour, serum creatinine >1.5 mg/dl, platelet count< 50,000/mm^3, gastrointestinal bleeding, necrotizing enterocolitis, and pulmonary hemorrhage, the patients were put on I .v acetaminophen as an alternative medication. All the patients were less than 15 days old and were given a maximum of 2 courses (if necessary) of the chosen drug, with the first course commencing within the 24 hours of the time of diagnosis and with each course taking three days. The dosage was 10 mg/kg/dose Q6h and 10 mg/Kg on the first day, followed by two doses of 5 mg/kg every 24 hours for i.v acetaminophen and oral ibuprofen, respectively.

The success of the selected drug in the management of PDA was defined either as a closed duct or a size less than 0.5 mm at the end of the treatment course.

Results

In 24 patients (48%), the PDA was closed, and in 15 patients (30%), the size of the duct became less than 0.5 mm, after one course of treatment. In the rest 11 patients (22%), the duct closed after the second course of treatment. As shown in Tables 1 and 2, the success rate for closing the PDA was similar in both groups, and there was no significant difference statistically.

As for the side effects, a significant difference (*P*=0.021) was seen between the two groups. These were more commonly seen in the group receiving oral ibuprofen, as demonstrated in Tables 3 and 4.

As demonstrated in Table 3, one side effect, i.e., BUN rise, was seen more commonly in the group who was on iv acetaminophen in contrast to other side effects, which were detected much more commonly in the other group.

Base on the above results, we conclude that although both treatments were successful in closing PDA since the side effects of acetaminophen were much less common than ibuprofen, the former had better be prescribed for pre-term neonates who suffer from a hs PDA.

Table 1. The total success rate

***P*=0.232**			**group**		**Total**
			A	**B**	
Success.treatment	**Closed**	**Count**	9	15	24
		% within group	36.0%	60.0%	48.0%
	Closing	**Count**	9	6	15
		% within group	36.0%	24.0%	30.0%
	Open & need to 2nd	**Count**	7	4	11
		% within group	28.0%	16.0%	22.0%
Total		**Count**	25	25	50
		% within group	100.0%	100.0%	100.0%

Table 2. The success rate after 1st and 2nd course of treatment

***P*=0.306**		**Group**		
		A	**B**	**Total**
Response after 1st	**Count**	18	21	39
	% within group	72.0%	84.0%	78.0%
Response after 2nd	**Count**	7	4	11
	% within group	28.0%	16.0%	22.0%

Table 3. The side effects in detail

Side.effect	**Bilirubin rise**	**Count**	**1**	**0**	**1**
		% within group	4.0%	.0%	2.0%
	Creatinin rise	**Count**	0	3	3
		% within group	0%	12.0%	6.0%
	IVH	**Count**	0	1	1
		% within group	0%	4.0%	2.0%
	GI bleeding	**Count**	0	1	1
		% within group	0%	4.0%	2.0%
	Enterocolitis	**Count**	0	1	1
		% within group	0%	4.0%	2.0%
	ALT or AST rise	**Count**	0	1	1
		% within group	0%	4.0%	2.0%
	none	**Count**	24	18	42
		% within group	96.0%	72.0%	84.0%
Total		**Count**	25	25	50
		% within group	100.0%	100.0%	100.0%

Table 4. The total side effects

***P*=0.021**		**Group**		
		A	**B**	**Total**
No	**Count**	24	18	42
	% within group	96.0%	72.0%	84.0%
Yes	**Count**	1	7	8
	% within group	4.0%	28.0%	16.0%
Total	**Count**	25	25	50
	% within group	100.0%	100.0%	100.0%

Discussion

Approaching the hemodynamically significant PDA has been a subject of great challenge among pediatric cardiologists during the past decade. First of all, which remaining ductus arteriosus should be considered as a hs PDA, and finally, how it must be managed: medically or surgically?

Nowadays, the hs PDA is defined based on the echo findings, as mentioned previously, and the presence of some symptoms describing the heart failure syndrome such as tachypnea, respiratory distress, poor feeding, and so on. After detecting a PDA as large enough to be closed, the next step would be the type of treatment to be chosen.

Pharmacotherapy seems to be the therapy of choice because of its safety and effectiveness in the treatment of hs-PDA in preterm infants (31). For many years, non-steroidal anti-inflammatory drugs (NSAIDs), mostly indomethacin and ibuprofen, have been used as the main therapeutic medications for closing hs-PDA. Despite the fact that NSAIDs have been very effective in closing patent ductus arteriosus in preterm neonates, the emergence of complications such as IVH, GI bleeding, BUN rise, enterocolitis, and so on, has been noticed and paid attention to by the physicians.

The role of acetaminophen as an alternative treatment for the closure of hs-PDA has gained importance in recent years due to these potential side effects (32).

We conducted a controlled clinical trial in 50 pre-term neonates, comparing the efficacy and side effects of parenteral acetaminophen and oral ibuprofen. Our study demonstrated that acetaminophen is as effective as ibuprofen in promoting ductal closure of PDA in preterm infants. The rate of closure in acetaminophen therapy (72%) was relatively near to that after ibuprofen (84%) therapy, with no significant difference statistically (*P*=0.232). This result was similar to those of other studies (33-35).

One last point that needs to be kept in mind is that fortunately, neonates tend to suffer less from the hepatotoxic effects of acetaminophen than do older children. This can be explained by the metabolism of acetaminophen that changes with age. In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. Hepatic glucuronidation is relatively immature at birth. The sulfate conjugate predominates in preterm infants, newborns, and young infants (36). With maturation, these clearance pathways for acetaminophen change. The usual adult ratio of 2:1 glucuronide to sulfate conjugates of acetaminophen is achieved by 12 years of age (37).

Our study suggests that intravenous acetaminophen is safe but not superior to oral ibuprofen in promoting closure of the hemodynamically significant PDA in preterm infants when treatment starts within 24 hours of diagnosis. As for the side effects, comparing those of parenteral acetaminophen and oral ibuprofen, we found that those of the former were less common than the latter, which was significant statistically (P=0.021). Therefore, based on our study, it seems rational to prescribe IV acetaminophen for preterm neonates with hs PDA as a first-line treatment in intensive care units.

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