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Paracetamol therapy in a preterm newborn with patent ductus arteriosus

To the Editor,

Patent ductus arteriosus (PDA) is a problem which is especially frequently observed in very low birth weight preterm newborns. Indomethacin and ibuprofen are used as medical therapies for closure of patent ductus arteriosus. However, these drugs may cause to some side effects. Surgical closure is performed in newborns who have a contraindication for medical treatment or when medical treatment is unsuccessful. However, some complications may be observed during surgical closure or following surgical closure (1,2). In this letter, a male preterm newborn whose PDA was not closed despite oral ibuprofen given for three times, but was markedly reduced hemodynamically with paracetamol treatment before surgical closure and who did not need surgical intervention was presented.

The APGAR score at the first and fifth minutes of a male newborn who was born by cesarean section with a birth weight of 820 g at 24 weeks and 5 days 48 hours after administration of betamethasone because of preterm delivery and oligohydramniosis from the first pregnancy of a 26-year-old mother were found to be 5 and 7, respectively. Complete blood count of the patient who was followed up while receiving mechanical ventilation at the 6th hour after delivery was as follows: WBC: 74 600/µL, hemoglobin 15.2 g/dL, platelets 417 000/µL, peripheral smear: polymorphonuclear leukocytes 44%, lymphocytes 18%, bands 12% (immature/mature cell ratio 0.27), monocytes 10%, promyelocytes 16%, toxic granulation, normoblasts 30%. No blastic cell was observed. With leukomoid reaction, toxic granulation and an immature/mature cell ratio of 0.27 early neonatal sepsis was considered and intravenous ampicillin and netylmycine were started at appropriate doses after obtaining regular cultures. Respiratory distress syndrome was not considered radiologically and clinically. Blood biochemical variables were evaluated to be normal. In the follow-up, antibiotherapy was discontinued, since the cultures remained negative and infection markers were found to be negative. On the fourth day after delivery the patient had no murmur, but Corrigan's pulse was found in the femoral arteries and FiO2 was >40%. Echocardiogram revealed a small secundum atrial septal defect. The ductus was closed and follow-up was recommended. On the 8th day after delivery, a 1/6 systolic murmur was heard on all cardiac areas. The repeated ECHO revealed a 2 mm PDA and a left atrium (LA)/aotric annulus (Ao) ratio of 1.5. Oral ibuprofen treatment was started. On the second day of treatment ibuprofen was discontinued because of development of thrombocytopenia (28000/µL). On the 11th day after delivery, his murmur continued, the platelet count was found to be 119000/µL and creatinine was found to be 0.8 mg/dL. The first oral ibuprofen treatment was administered at a dose of 10/5/5 mg/kg/day with 24 hour intervals. The ECHO performed after the first treatment revealed a ductus diameter of 2 mm and a LA/Ao ratio of 1.4. Two courses of oral ibuprofen treatment at the same dose were given to the patient who was found to have hemodynamically significant PDA. Despite this treatment hemodynamically significant PDA persisted. After obtaining written consent from the family oral paracetamol treatment (15 mg/kg/dose, every 6 hours, for 72 hours) was given on the 20th day after delivery before surgical intervention. Complete blood count, peripheral smear and liver function tests were found to be normal before and after paracetamol treatment. On ECHO performed after treatment, it was observed that the ductus diameter was reduced to 1 mm and the LA7Ao ratio was reduced to 1,1 and follow-up was recommended. No murmur was heard in the patient on the 47th day after delivery. On the 75th day, the ductus was closed completely (Table 1). In the follow-up of the patient who had no intracranial bleeding, severe bronchopulmonary dysplasia and grade-1 retinopathy of prematurity developed. The patient was discharged on the 108th day after delivery without oxygen (oxygen saturation>90%) and was started to be followed up in the neonatology outpatient clinic.

Medical treatment is started in symptomatic PDA patients with hemodynamically significant ECHO findings (LA/Ao

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Table 1. Follow-up of PDA closure treatment

Postnatal age (days)	Murmur	Ductus diameter	LA/Ao (mm)	Treatment	Course (mg/kg/dose)
4	-	Kapalı	1	Follow-up	-
8	+	2	1.5	Oral ibuprofen	10/-/-
11	+	2	1.5	Oral ibuprofen	10/5/5
13	+	2	1.4	Oral ibuprofen	10/5/5
17	+	Echocardiography was not performed		Oral ibuprofen	10/5/5
20	+	2	1.5	Oral paracetamol	15 (Every 6 hours) A total of 12 doses
22	+	1.5	1.1	Follow-up	-
25	+	1	1.1	Follow-up	-
28	+	1	1.1	Follow-up	-
34	+	1	1.1	Follow-up	-
47	-	1	1	Follow-up	-
75	-	Closed	-	-	-

LA: Left atrium, Ao: Aortic annulus

>1.4, ductus diameter >1.4 mm) (1). Since indomehtacin may lead to complications including transient or persistent renal dysfunction, necrotizing enterocolitis and decreased oxygen supply to the brain, researchers have tended towards a safer pharmacological agent (3,4). It was shown that ibuprofen which is another cyclooxygenase inhibitor had fewer brain, renal and mesenteric side effects, increased the autoregulation of the brain blood flow and preserved neurologic functions following oxidative stress in animal experiments (5,6,7). In a study performed in our country, it was reported that oral ibuprofen treatment was as efficient as intravenous indomethacin treatment and even more efficient than that in closure of PDA (8).

In cases where medical treatment is contraindicated or unsuccessful, surgical ligation is performed for closure of patent ductus arteriosus. Complications including recurrent laryngeal nerve damage, chylothorax, pneumothorax, left ventricular dysfunction and scoliosis may be observed in relation with surgical closure (1).

Because of potential complications of medical and surgical closure treatments researchers have tended towards novel searches. With this aim paracetamol which is a novel agent in PDA treatment has been started to be used (9,10). Paracetamol acts by inhibiting the peroxidase component of prostaglangin synthetase. Hammerman et al. (9) reported for the first time that the ductus closed or was reduced in all the patients in the first three days with oral paracetamol treatment given at a dose of 15mg/kg/dose every 6 hours in 5 patients whose PDA was not closed with two courses of ibuprofen treatment or who had contraindications for ibuporfen treatment and no side effects was observed. The second study was conducted in our country and reported that success with a rate of 87.5% was obtained with paracetamol treatment given to 8 patients with the same justifications (10). Based on these two studies, we administered paracetamol treatment for 72 hours at the same dose before surgical intervention to our patient whose PDA was not closed with three courses of oral ibuprofen treatment. ECHO performed after treatment revealed that the ductus was hemodynamically regressed and reduced with a marked degree. No side effect was found during treatment. In the follow-up, patent dustus was reduced in size and was observed to be insignificant hemodynamically on follow-up ECHOs performed. It was found that the ductus was completely closed on the 75th day after delivery.

Based on this case presentation, we think that the chance of paracetamol treatment before surgical intervention should be given to very low birth weight preterm newborns whose PDAs do not close with recurrent ibuprofen treatment.

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