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RESEARCH ARTICLE

Is medical therapy succesful in hemodynamically significant patent ductus treatment in term newborns?

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ABSTRACT

Aim: To investigate the clinical success of medical patent ductus arteriosus closure treatment for hemodynamically significant patent ductus arteriosus in term babies.

Methods: Our study included patients treated in two neonatal intensive care units with hemodynamically significant patent ductus arteriosus after the 3rd postnatal day and administered medical patent ductus arteriosus closure treatment (ibuprofen and paracetamol) at the discretion of the pediatric cardiologists while awaiting referral for surgical closure treatment.

Our retrospective analysis included anthropometric measurements at birth, the day treatment started postnatally, and other existing clinical conditions that might influence the prognosis of patent ductus arteriosus. Then, treatment success was evaluated by echocardiographic results.

Results: We included all ten patients diagnosed with hemodynamically significant patent ductus arteriosus and administered medical treatment with a mean gestational age at birth of 38.4 ± 1.21 weeks, and median birth weight of 3125 grams (3005-3200). We started medical closure treatment at mean postnatal 11.6 ± 4.9 days with ibuprofen (70%, n=7) or paracetamol (30%, n=3). 40% (n=4) of the infants had complete closure, 20% (n=2) became asymptomatic, and 10% (n=1) underwent surgical ligation. 30% (n=3) of patients died due to different complications during surgical preparation. As we defined treatment success as complete or partial closure and compared paracetamol and ibuprofen success, there was no statistically significant difference between them (p=0.5).

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Conclusion: Medical closure treatment might be effective in the presence of hemodynamically significant patent ductus arteriosus in term infants. There was no statistical superiority of paracetamol or ibuprofen treatments over each other in terms of treatment success.

Keywords: newborn, patent ductus arteriosus, ibuprofen, paracetamol

INTRODUCTION

The ductus arteriosus is a vascular structure in fetuses that connects the junction of the common pulmonary and the left pulmonary arteries to the descending aorta, which creates a vital outlet channel that flows from the right-ventricular outlet to the systemic circulation to prevent high resistance in the pulmonary arterial circulation by connecting the pulmonary and systemic circulation in the fetus (1,2).

An increase in systemic vascular resistance results in the obliteration of the fetal shunts following placental discharge. The closure mechanisms of the ductus arteriosus have two milestones. The first mechanism is the spontaneous closure of the ductus arteriosus induced by the onset of pulmonary respiration at birth, which results in increased oxygenation with the increase in partial oxygen pressure in the blood and loss of vasodilators due to decreased prostaglandin E2 production and its receptors (3). The other mechanism is that the elastic fibers of the ductus arteriosus, unlike the large arteries, are fewer, and the vessel cannot return to its initial state after vasoconstriction (4).

Following birth, spontaneous closure occurs in 8-22% of preterm babies born at 24-28 weeks of gestation, while this rate increases up to 90% at the 30th week of gestation and nearly 100% in term babies (5). Ductus arteriosus closure is complete within the first three days of life in term healthy neonates (2). The term patent ductus arteriosus defines circumstances in which spontaneous closure of the ductus arteriosus is delayed (1). The incidence of patent ductus arteriosus is between 2.9 and 7.8 per ten thousand term-born babies (6,7).

There are several risk factors for patent ductus arteriosus in premature babies, such as low birth weight, respiratory distress syndrome, being not treated with antenatal corticosteroids, chorioamnionitis, postnatal fluid overload/error in fluid management, sepsis, intrauterine growth retardation, genetic factors, perinatal asphyxia, being born at high altitude, and genetic predisposition (5,8). A neutral temperature environment, adequate oxygenation, use of high positive end-expiratory pressure (>5 cmH2O), short inspiratory time (0.35 sec), keeping the hematocrit level between 35-40%, and fluid restriction (while avoiding dehydration) are the targets. Therefore, prostaglandin inhibition via cyclooxygenase inhibitors is the mainstay of therapy for patent ductus arteriosus closure in premature infants (9). Currently, indomethacin, ibuprofen (intravenous or oral), or paracetamol are efficacious for the medical closure treatment of patent ductus arteriosus, with indomethacin and ibuprofen having 70-80% success rate in preterm infants (5).

Elimination of pulmonary-hyper circulation and prevention of obstructive pulmonary vascular disease, endocarditis, and endarteritis are the indications and treatment goals of patent ductus arteriosus closure treatment (10). Apart from medical closure treatment, patent ductus arteriosus occlusion with transcatheter devices can also be applied. Complications of this treatment include device embolization into the pulmonary or systemic circulation unanticipatedly and creating a coarctation in the aorta. Device-related obstruction of the aortic (forming iatrogenic coarctation) or pulmonary flow, transient left ventricular systolic dysfunction, hemolysis, and recanalization may occur, especially in young infants. Complications are more common in infants with a body weight of less than 6 kg (10).

Percutaneous occlusion is preferable to surgical ligation in infants and children weighing ≥6 kg as it is less invasive than surgical treatment and does not result in a surgical scar (6,7). Still, complications of transcatheter patent ductus arteriosus closure treatment are more common in infants weighing less than 6 kg (10). However, surgical ligation is also a safe and effective alternative (8), but the efficacy

of pharmacological treatment in term infants is not known. Therefore, the purpose of this study was to present the responses of term infants with hemodynamically significant patent ductus arteriosus who had been treated with paracetamol and ibuprofen while waiting for surgical closure.

MATERIALS AND METHODS

We conducted this study in two centers (Marmara University, Faculty of Medicine and Gungoren Hospital) between January 2017 and December 2020. We included all term babies diagnosed with hemodynamically significant patent ductus arteriosus according to the American Academy of Pediatrics guidelines (11). Patients had tachycardia, tachypnea, need for respiratory support, abdominal distension, systemic systolic dysfunction, or echocardiographic features (severe left atrial or ventricular dilatation, systolic left ventricular dysfunction, ductus diameter ≥2 to 3 mm, and ductal left-to-right diastolic flow ≥0.5 m/s.) after the third postnatal day. We started medical therapy with the approval of the pediatric cardiologists for hemodynamically significant patent ductus arteriosus in patients awaiting referral for surgical closure treatment. We used ibuprofen 10-5-5 mg/kg/day for three days or paracetamol 4x15 mg/kg/dose for five days with peroral or intravenous ways if we could not give ibuprofen due to their clinical conditions like renal failure, gastrointestinal bleeding, and thrombocytopenia.

Our study included anthropometric measurements of the patients at birth, other existing clinical conditions that may affect the prognosis, the postnatal treatment day and drug type, and evaluated the clinical response with echocardiography. We defined complete closure as total closure of the ductus arteriosus on echocardiography and partial closure as the remission of the hemodynamically significant patent ductus arteriosus to less than 1.5 mm in diameter, resulting in normalization of left heart load and increased pulmonary circulation with improvement of systemic hypoperfusion.

The ethical approval for this study was obtained from Marmara University Faculty of Medicine Clinical Research Ethics Committee (09.2022.25). We conducted the study following the ethical principles of the Declaration of Helsinki. As this was a retrospective study, informed consent was not required.

Statistics

We presented continuous data as mean +/- standard deviation or median (interquartile range) according to the distribution pattern. Fisher's exact test was used to compare two groups of categorical variables. A p-value <0.05 was considered statistically significant. We used the Jamovi 2.2.5 package program for statistical analyses.

RESULTS

Ten patients were eligible for the study. The median birth weight, the mean gestational week at birth, length, and head circumference were 3125 grams (3005-3200), 38.4+/-1.21 weeks, 49+/-1.94 cm, and 36+/-3.5 cm, respectively. 90% (n=9) of the patients were born by cesarean section and 10% (n=1) by normal-spontaneous vaginal delivery. In addition, 10% (n=1) of the babies had persistent pulmonary hypertension and 20% (n=2) had a ventricular septal defect (VSD).

We administered ibuprofen to 70% (n=7) of the patients and paracetamol to 30% (n=3). The mean postnatal day of initiation of medical treatment for patent ductus arteriosus closure was 11.6 +/-4.9 days. We observed complete hemodynamically significant patent ductus arteriosus closure in 40% (n=4) and partial closure in 20% (n=2) of the patients. We discharged these patients after treatment and referred them to the pediatric cardiology outpatient clinic. Unfortunately, 40% of the remaining babies did not respond to the treatment, and we referred them for surgical closure. One patient who underwent surgical ligation survived, while the other three died due to various complications (table 1). We administered ibuprofen to 70% (n=7) of the patients and observed total or partial closure in 71% (n=5) of them, while the closure rate was 33.3% (n=1) of the patients who received paracetamol (30%, n=3).

We defined treatment success as complete or partial closure. There was no statistically significant difference

between paracetamol and ibuprofen therapy regarding treatment success (Fisher's exact test, p=0.5).

Table 1 describes the clinical characteristics and treatment responses of all patients.

DISCUSSION

There is no consensus on the efficacy of prostaglandin synthesis inhibitors (indomethacin and ibuprofen) for medical patent ductus arteriosus closure in term newborns; however, the recent pharmacological closure of a patent ductus arteriosus in a term newborn with indomethacin (9) suggests that this issue needs further investigation. In addition, since the risk of complications is higher in patent ductus arteriosus closure with the percutaneous transcatheter method, especially in infants weighing <6 kg, the literature recommends postponing interventional closure if possible and evaluating pharmacological treatment options beforehand (5).

Besides indomethacin and ibuprofen, there is evidence for the efficacy of paracetamol treatment in closing patent ductus arteriosus in preterm neonates (2). A study examined the efficacy of oral paracetamol to close the patent ductus arteriosus effectiveness of in preterm infants (25.7+/-1.5 weeks; 724 +/- 143 grams) in whom ibuprofen cannot be used or was ineffective and evaluated partial closure (at least 50%) and non-closure rates. They reported that they observed complete closure in 50% and a significant reduction in hemodynamic shunt in 20% of patients (12).

There are conflicting results from studies evaluating the efficacy of pharmacological patent ductus arteriosus closure treatments in term infants. A study reported that 5-day oral ibuprofen treatment (doses: 10, 5, 5, 5, 5 mg/kg/day, respectively) had no statistical effect on patent ductus arteriosus closure rate in term newborns compared to placebo. They found that patent ductus arteriosus was closed in 65% of the patients in the oral ibuprofen group and 50% in the placebo group (13). In a similar study, researchers started oral ibuprofen (10, 5, and 5 mg/kg/day for three days, respectively) in 8-14 days-old term infants with patent ductus arteriosus in the intervention group and compared it with the control patients. The patent ductus arteriosus was closed in 62.9% of the patients taking oral ibuprofen and 54.3% in the control group, and there was no statistically significant difference between them (14). However, the researchers did not give detailed information about the hemodynamic insufficiency of these cases in these publications.

Another option is the closure of hemodynamically significant patent ductus arteriosus with the transcatheter device, and the success rate is 94.3% in infants below 6 kg (15). However, there is a risk of 12.6% major adverse events (most frequently acute

Table 1. Clinical features and treatment responses of the patients.

	GW	BW	PN day	Drug	Result (hsPDA)	Additional diagnosis	Survival
1	39	3200	15	Ibuprofen	Closed	Down syndrome	Survived
2	38+6/7	3090	20	Ibuprofen	Asymptomatic	Hydrancephaly	Survived
3	40	2150	19	Ibuprofen	Not closed	Esophageal atresia	Exitus
4	37+2/7	3200	8	Ibuprofen	Closed	-	Survived
5	38	3250	9	Paracetamol	Not closed	PNA	Exitus
6	38+4/7	3050	10	Paracetamol	Not closed	PNA+Down syndrome	Exitus
7	36	2990	11	Ibuprofen	Asymptomatic	-	Survived
8	40	2250	11	Ibuprofen	Need surgery	-	Survived
9	38	3160	8	Paracetamol	Closed	-	Survived
10	38	3640	5	Ibuprofen	Closed	Immunodeficiency	Exitus

*All patients were intubated and were taking at least one inotropic drug. GW: gestational week (week), BW: birth weight (grams), PN day: postnatal day of treatment, hsPDA: hemodynamically significant patent ductus arteriosus, PNA: perinatal asphyxia

arterial damage (3.5%) and device-embolization (2.4%) secondary to this procedure, and the probability of major adverse events is higher in infants younger than thirty days (15). In addition, this study reported that the risk of developing embolization is higher in babies with excessive and low birth weight (15). Therefore, the substantial rate of occurrence of major adverse events related to transcatheter closure and the existence of centers that cannot perform patent ductus arteriosus closure by transcatheter route make it necessary to apply pharmacological patent ductus arteriosus closure treatment before applying for surgical ligation and to switch to transcatheter or surgical patent ductus arteriosus closure treatment by the way in cases refractory to pharmacological therapy.

We detected complete patent ductus arteriosus closure after intravenous paracetamol (n=1) and ibuprofen (n=3) treatment in four patients, also, hemodynamically significant patent ductus arteriosus became asymptomatic in two patients. Unfortunately, three patients awaiting the operation had a multiorgan failure and died due to severe perinatal asphyxia (2 patients) and complications of esophageal atresia (one patient). In addition, one patient died later due to immunodeficiency, but echocardiographic and clinical follow-up revealed that the patent ductus arteriosus was closed.

These results suggest that intravenous paracetamol and ibuprofen treatment may be beneficial in the absence of contraindications while awaiting referral or operation/intervention in centers where emergency transcatheter or surgical intervention is not available.

CONCLUSION

Pharmacological closure of hemodynamically significant patent ductus arteriosus seems possible in term infants. In selected cases, medical treatment may be an option before surgical or transcatheter occlusive treatment. In this case series, we did not find a statistical superiority of paracetamol or ibuprofen treatments to each other in terms of hemodynamically significant patent ductus arteriosus closure. Prospective randomized controlled studies in large case series are needed to provide more conclusive evidence.

Ethical approval

This study has been approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (approval date 07.01.2022, number 09.2022.25). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: AY, İK, ZAÜ, SGK, MTK, AÇM; Concept: İK, MTK, AÇM; Design: AY, İK, ZAÜ, SGK, MTK, AÇM; Data Collection or Processing: AY, İK; Analysis or Interpretation: İK, MTK, AÇM; Literature Search: AY, İK, ZAÜ, SGK, AÇM; Writing: AY, İK, ZAÜ, SGK, MTK, AÇM. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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