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Comparison of Mortality and Morbidity in Syrian and Turkish Premature Babies with Patent Ductus Arteriosus

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Abstract

Background: Having observed that the clinical course of premature infants at the 28th gestational week and earlier followed-up in our department was different between races, we aimed to examine the effect of the genetic structure on patent ductus arteriosus (PDA) regarding morbidity and mortality among Turkish and Syrian babies.

Methods: This single-center, retrospective study was carried out with 43 Turkish newborns (group 1) and 31 Syrian newborns (group 2) with a gestational age of 28 weeks or less who had been followed-up between February 2016 and March 2018 in our department after exclusion of the risk factors that may affect ductus arteriosus, and compared the morbidity and mortality of the study groups.

Results: The diameter of the duct, the left atrium/aortic root ratio, the need for ductus occluding intervention, bronchopulmonary dysplasia, hospital stay and mortality rate were significantly higher in Syrian newborns (group 2).

Conclusion: The higher morbidity and mortality rate of PDA in our Syrian patients may be related to the low socioeconomic level resulting from the war in Syria or the difference in the genetic structure.

Keywords: Ductus arteriosus, race, genetic factors

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Introduction

Patent ductus arteriosus (PDA) is one of the most common cardiovascular diseases with an incidence of 27% among newborns at or below 28th gestational weeks.[1] According to the presence and hemodynamic effects of PDA, it may cause a number of morbidities including pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), decrease in cerebral oxygenation and neurodevelopmental maturation disorder, intraventricular hemorrhage (IVH), acute renal failure, nutrition intolerance, necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), sepsis and longer hospital stay, and even mortality.[2,3]

The most important risk factors that cause the ductus arteriosus to remain open are the gestational week and low birth weight. Besides, respiratory distress syndrome, antenatal steroid use, chorioamnionitis, fluid management, sepsis, small for gestational age (SGA) baby, genetic factors and drug use are other risk factors.[4-11]

Although the incidence, morbidity and mortality rates of PDA have been reported country by country in previous studies, there are few studies on the genetic factors belonging to different races. As we observed that the clinical course of premature infants at 28th gestational week and earlier followed-up in our department was different between races, we decided to compare Syrian and Turkish premature newborns with PDA in terms of morbidity and mortality, and aimed to explore the effect of genetic structure on the PDA outcome.

Materials and Methods

This single-center and retrospective study was carried out with 78 Turkish newborns (group 1) and 71 Syrian newborns (group 2) with a gestational age of 28 weeks or less who had been followed-up in our department between February 2016 and March 2018. Seventy-five babies with risk factors, who have been presented in Figure 1, causing the duct to remain patent, were excluded from the study to determine the effect of the race factor.

Transthoracic echocardiography was performed routinely within the first 24-72 hours of life according to the recommendation of the Turkish Neonatology Association for newborns with a gestational age of 28 weeks or less.[12] Echocardiographic examinations were performed using the Vivid S6 Echocardiography System (General Electric's Healthcare, Milwaukee, WI). The ductal inner diameter and left atrial (LA)/aortic root (Ao) ratio were measured by echocardiography. The ductus diameter/body weight ratio of >1.4 mm/kg and LA/Ao ratio of >1.5 were considered hemodynamically significant PDA (hsPDA).[12] Peroral treatment with oral acetaminophen was administered at a dose of 15 mg/kg, every 6 hours for three days, or ibuprofen at a dose of 10 mg/kg in the 1st day, 5 mg/kg in the 2nd day, and 5 mg/kg on the 3rd day orally.

The patients' gestational age, birth weight, gender, ductus diameter, LA/Ao ratio, whether or not the patient had received medical treatment for PDA closure (if so, which drug was administered), and the diagnoses of IVH, NEC, BPD and ROP were noted at discharge or death age. Diagnosis of NEC was established according to the Modified Bell's criteria[13]; the diagnosis of IVH was based on the Papile classification[14], the ROP diagnosis was made according to the criteria of the International ROP Classification Committee[15], and BPD was according to oxygen requirement at the 36th postmenstrual week.

Statistical Analysis

Statistical analyses were performed using the statistical package SPSS for Windows version 17.0 (SPSS Inc., Chicago, Illinois). The paired samples t-test and independent samples t-test were used for continuous variables. The chi-square test was used for categorical variables. Continuous variables are presented as the mean ± SD, and categorical variables are given as frequencies and percentages. A p value of less than 0.05 was considered statistically significant.

Results

During the course of our study between February 2016 and March 2018, a total of 43 Turkish (group 1)

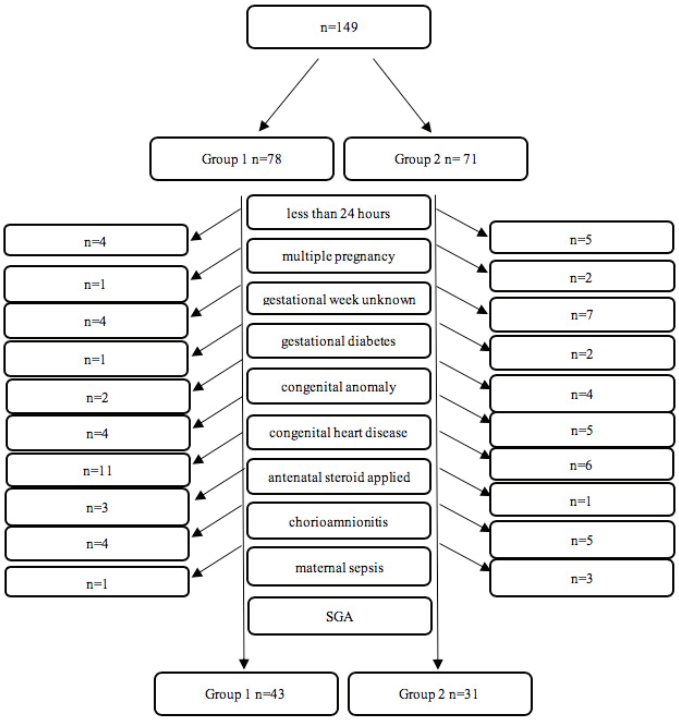

Figure 1. Flowchart of study
SGA: Small for gestational age

and 31 Syrian (group 2) newborns who had been born at 28 weeks of gestation or less were included in the study. The two groups were compared in terms of natal period characteristics (Table 1). There was no difference in gestational age, birth weight, sex, type of delivery and APGAR scores between the study groups (p>0.05, for all; Table 1).

When the echocardiography findings and the treatment results of PDA were compared, we found that the ductus diameter was larger, the LA/Ao ratio was higher, and the requirement for ductus closure treatment was more frequent in Syrian infants (p<0.05, for all; Table 2).

There was no difference between the two groups in terms of surfactant requirement, ventilation support requirement and type of ventilation (p>0.05, for all; Table 3).

When the study groups were compared in terms of morbidity and mortality; the frequency of BPD, length of hospital stay and mortality rate of the babies in group 2 were significantly higher than those in group 1 (p<0.05, for all; Table 4).

Table 1. Comparison of the natal parameters between group 1 and group 2

Parameter	Group 1	Group 2	p value
Gestational age (weeks)	26.81±1.12	26.73±0.96	0.07
Birth weight (gr)	969±287	921±274	0.23
Sex (male/female)	24/19	18/13	0.18
Mode of delivery (C/S, VD)	27/16	23/8	0.63
APGAR 1'	7.06±0.66	6.31±0.89	0.54
APGAR 5'	8.23±0.57	6.77±0.36	0.77

C/S: Caesarean section delivery, VD: Vaginal delivery

Table 2. Comparison of patent ductus arteriosus parameters between group 1 and group 2

Parameter	Group 1	Group 2	p value
Postnatal age of diagnosis	2.3±1.2	1.4±0.5	0.01
Ductal diameter	1.82±0.56	2.4±0.75	0.02
LA/Ao ratio	1.36±0.26	1.87±0.59	0.01
Closed without treatment	21 (48.8%)	8 (25.8%)	0.01
Ductal non-surgical closure	22 (51.2%)	23 (74.2%)	0.03
Ductal surgical closure	0	0	-

LA/Ao: Left atrium to aortic root ratio

According to these results, the mortality and morbidity of the newborns with PDA in group 2 were higher.

Discussion

One of the most important factors contributing to morbidity and mortality among the newborns is hsPDA. The relation of hsPDA, which is diagnosed echocardiographically, with some morbidities, particularly chronic lung disease, and even mortality, has been investigated in recent years. During the follow-up of very low birth weight newborns admitted to our department in the last three years, we observed that the incidence and severity of PDA, medical treatment requirement for ductus closure, and the morbidity and mortality rates

Table 3. Comparison of respiratory support between group 1 and group 2

Parameter, n (%)	Group 1	Group 2	p value
Received surfactant	37 (86%)	30 (96.7%)	0.91
HFV	3 (6.9%)	3 (9.6%)	0.47
CMV	34 (79%)	27 (87%)	0.83
nCPAP	6 (13.9%)	1 (2%)	0.52
Received dexamethasone	4 (9.3%)	3 (9.6%)	0.33

HFV: High frequency ventilation, CMV: Conventional mechanical ventilation, nCPAP: Nasal continuous positive airway pressure

Table 4. Comparison of patent ductus arteriosus outcome between group 1 and group 2

Parameter, n (%)	Group 1	Group 2	p value
Nosocomial sepsis	11 (25.5%)	7 (22.5%)	0.36
IVH	8 (18.6%)	8 (25.8%)	0.12
NEC	4 (9.3%)	4 (12.9%)	0.73
ROP	2 (4.6%)	2 (6.4%)	0.53
BPD	7 (16.3%)	11 (35.4%)	0.01
Duration of hospital stay (days)	67.4±21.3	79.7±34.8	0.03
Death	6 (13.9%)	9 (29%)	0.01

IVH: Intraventricular hemorrhage, NEC: Necrotizing enterocolitis, ROP: Retinopathy of prematurity, BPD: Bronchopulmonary dysplasia

were higher in Syrians newborns. Thus, we compared the Turkish and Syrian newborns with a gestational age of 28 weeks or less in terms of morbidity and mortality. There was no difference in gestational age, birth weight, sex, type of delivery and the APGAR score between the two groups, whereas we found that PDA was more severe, and the incidence of BPD, the length of hospital stay and the mortality rate were higher in Syrian infants. The PDA became symptomatic earlier, and the ductus diameter and the LA/Ao ratio were higher in group 2. Previous studies have demonstrated the relationship between the ductus diameter and morbidity and mortality. Schena et al. reported that the amount and duration of the ductal shunt were associated with the length of hospital stay, the development of BPD and mortality.[16] Sehgal et al. developed a ductal staging system using functional echocardiography on 372 preterm infants born before the 32nd gestational week and found that BPD and mortality increased as the stage increased.[17] Sellmer et al. reported that as the PDA diameter increased, the frequency of IVH, BPD and mortality also increased.[18] Although these studies do not establish a causal relationship between PDA and mortality, the most commonly accepted view suggests that the morbidity and mortality increase as the amount of shunt increases. In our study, the presence and severity of PDA and the amount of shunt were higher together with a longer hospital stay and higher BPD and mortality rates in the Syrian babies. Although the factors that may affect the presence and severity of PDA (gestational age, birth weight, antenatal steroid use, chorioamnionitis, early sepsis, SGA), were similar between the two groups, the most probable explanation for the higher severity of PDA and the medical treatment requirement for ductus closure in group 2 was the difference in the genetic structure.

Although many studies have been conducted on the diagnostic methods and treatment options of PDA, there is a limited number of previous researches investigating the genetic basis of PDA. Human and animal studies on this subject focus on the genetic loci that may result in increased susceptibility to PDA. Treszl et al. showed that AT1R CC genotype of PDA developed at a lower rate than the AA and AC genotype.[19] In a study by Petrova et al. comparing the newborns from black, white, Hispanic and other races with a gestational age of 32 weeks and below, they showed that the mortality of black newborns with the same gestational age and birth weight was lower than that of others.[20] Li et al. showed that PRDM6 mutations caused larger PDAs.[21] Zidan et al. and Zhu et al. found that the C677T allele of the *MTHFR* gene was associated with atrial septal defect and PDA.[22,23] In another study by Dagle et al., genetic mutations of transcription factor activating protein-2, tumor necrosis factor receptor-associated factor 1 and prostacyclin synthase were found to be associated with PDA.[24] Waleh et al. showed that the expression of SLCO2A1 and NOS3 decreased the success of indomethacin and ibuprofen in ductus closure by increasing the prostaglandin synthesis

in the Caucasian race.[25] Waleh et al. demonstrated that three calcium and potassium-channel genes (*CACNA1G/alpha1G*, *CACNB2/CaL-beta2*, and *KCNA2/Kv1.2*), were associated with prostaglandin inhibition and emphasized the consideration of these genes in the development of future medical treatment strategies for PDA closure.[26] In another study, Mangones et al. investigated the prevalence of congenital heart diseases (CHD) and showed that PDA was most commonly seen in non-hispanic whites.[27] In their study with 200 patients with CHD, Qiao et al. found that MEF2C mutation was associated with PDA.[28] These previous studies suggest that the incidence and severity of PDA differ from race to race due to some kinds of mutations and differences in genetic structures, and the genetic structure even determines the success rate of the drugs used in the medical treatment for closure.

In our study, we observed that the ductus was usually wider in Syrian babies, and it is known that the larger ductus results in hemodynamically more severe shunt and increased morbidity and mortality. The reason for the ducts being wider in Syrian infants may be due to the different genetic structures mentioned above in these infants. Therefore, it is reasonable that the genetic coding of premature Syrian babies can lead to larger PDAs and consequently lead to higher mortality rates.

Conclusions

Although the risk factors were similar in both groups, we found that the presence and severity of PDA and consequently the morbidity and mortality related to PDA were higher among Syrian patients in our study. We think that this difference may be due to the low socioeconomic level resulting from the war in Syria or the difference in genetic structure. We believe that an important risk factor for PDA is the genetic structure of the individual and that a decrease in the uncertainty of genetic structure with future studies will lead to changes in the diagnosis and treatment of PDA and increase the success rate and survival.

Disclosure and conflicts of interest: The authors declare no conflict of interest.

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