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Congenital Heart Disease Requiring Maintenance of Ductus Arteriosus in Critically Ill Newborns Admitted at a Tertiary Neonatal Intensive Care Unit

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Abstract

Introduction: Congenital heart diseases (CHD) have been reported to be responsible for 30 to 50% of infant mortality caused by congenital disabilities. In critical cases, survival of newborns with CHD depends on the patency of the ductus arteriosus (PDA), for maintaining the systemic or pulmonary circulation. The aim of the study was to assess the efficacy and side effects of PGE (prostaglandin E) administration in newborns with critical congenital heart disease requiring maintenance of the ductus arteriosus.

Material and method: All clinical and paraclinical data of 66 infants admitted to one referral tertiary level academic center and treated with Alprostadil were analyzed. Patients were divided into three groups: Group 1: PDA dependent pulmonary circulation (n=11) Group 2: PDA dependent systemic circulation (n=31) Group 3: PDA depending mixed circulation (n=24)

Results: The mean age of starting PGE1 treatment was 2.06 days, 1.91 (+/-1.44) days for PDA depending pulmonary flow, 2.39 (+/-1.62) days for PDA depending systemic flow and 1.71 (+/1.12) for PDA depending mixing circulation. PEG1 initiation was commenced 48 hours after admission for 72%, between 48-72 hours for 6%, and after 72 to 120 hours for 21% of newborns detected with PDA dependent circulation. Before PEG1 initiation the mean initial SpO2 was 77.89 (+/- 9.2)% and mean initial oxygen pressure (PaO2) was 26.96(+/-6.45) mmHg. At the point when stable wide open PDA was achieved their mean SpO2increased to 89.73 (+/-8.4)%, and PaO2 rose to 49 (+/-7.2) mmHg. During PGE1 treatment, eleven infants (16.7%) had apnea attacks, five children (7.5%) had convulsions, 33 (50%) had fever, 47 (71.2%) had leukocytosis, 52 (78.8%) had edema, 25.8% had gastrointestinal intolerance, 45.5% had hypokalemia, and 63.6% had irritability.

Conclusions: For those infants with severe cyanosis or shock caused by PDA dependent heart lesions, the initiation and maintenance of PGE1 infusion is imperative. The side effects of this beneficial therapy were transient and treatable.

Keywords: prostaglandins, patent ductus arteriosus, congenital heart disease

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Introduction

Congenital heart diseases are the most common birth defects in newborns. Nearly 1% of newborns have congenital heart defects, and approximately one-quarter of those defects are associated with a critical condition [1-3]. Most of these heart defects require ductal patency for survival, and may not have been visible clinical signs immediately after birth until constriction of the duct occurred [4].

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Congenital heart diseases are responsible for 30-50% of infant mortality caused by birth defects. According to the NBDPN surveillance data, these deaths occurred most commonly in critical cases of hypoplastic left heart syndrome, transposition of the great arteries, or tetralogy of Fallot [5].

Prenatal diagnosis of cardiac malformations is crucial to initiate the most appropriate therapeutic strategy and depends on largely upon the echocardiography recognition of the structural heart defects during the second trimester [6,7].

According to Cochrane Database of Systemic Reviews 2014, infants with critical congenital heart defects that are dependent on the patency of the ductus arteriosus (PDA) for survival can be categorized into three groups. The first group is characterized by severe restriction of the pulmonary blood flow e.g. pulmonary atresia, tricuspid atresia or tetralogy of Fallot with pulmonary atresia. In these cases, pulmonary circulation is dependent on the patency of the ductus arteriosus and postnatal constriction of the ductus causes severe hypoxemia, cyanosis and death [8]. Group two includes conditions with severe restriction of the systemic blood flow e.g. severe aortic stenosis, coarctation of the aorta, interrupted aortic arch or left hypoplastic syndrome. In these cases, the systemic circulation is dependent on the patency of the ductus arteriosus and postnatal constriction of the ductus may cause systemic hypoperfusion, circulatory deterioration, metabolic acidosis, shock, and death [9]. The third group includes cardiac anomalies e.g. transposition of the great arteries, where adequate mixing of pulmonary and systemic blood flow is necessary for maintaining a circulation in series [10].

Due to its importance in the maintenance of the ductus patency during fetal life, prostaglandin is the elective therapy (PEG1) indicated for the temporary management of the neonate with ductus dependent congenital heart disease to maintain ductal patency until surgery can be performed [11]. PEG1 promotes vasodilatation by the direct effect on the vasculature and smooth muscle of the ductus arteriosus. Four PGE1 receptors have been identified. EP2 and EP4 receptor subtypes mediate PGE1-induced relaxation of the ductus arteriosus in human neonates through a cyclic AMP-dependent mechanism. PEG1 was approved by the Food and Drug Administration in 1981 for use in infants with a congenital cardiac defect but is not without limitation and side effects [12]. Sixty to eighty percent of PEG1 is metabolized on first passing through the lungs and so must be administered by continuous infusion. At a starting dose of 0.025 to 0.1 microgram/kg/minute, the ductus usually reopens within thirty minutes to two hours of initiating PGE1, with the clinical response usually being instant [11,13-15].

The aim of the study was to assess the efficacy and the effects of PGE administration in newborns with critical congenital heart disease requiring maintenance of ductus arteriosus.

Method

The clinical case reports of sixty-six infants admitted to one tertiary level academic center and treated with Alprostadil for critically congenital cardiac malformations from 1st January 2014 to 30st June 2016 were reviewed.

Patients were divided into three groups: Group 1: PDA dependent pulmonary circulation (n=11) Group 2: PDA dependent systemic circulation (n=31) Group 3: PDA depending mixing circulation (n=24)

A critical congenital heart defect was defined as a structural malformation of the heart present at birth, was life threatening and required interventions in the first months of life. Adverse medical events were defined as any unanticipated or undesirable incident that occurred during the treatment, or preparatory stabilization time before surgical treatment and might have necessitated an alteration in therapy.

Descriptive statistics including mean (+/-SD) were presented for continuous variables and frequencies for categorical variables. Univariate analyses with independent samples t-test and λ^2 test for categorical variables were performed to evaluate differences between group using SPSS 10.0 for Windows.

The significant level was set at α=0.05.

The study was conducted by the principles stipulated in the Declaration of Helsinki and informed consent for future data processing was obtained from the parents prior to data collection.

Results

During the study period, sixty-six neonates with congenital heart disease with PDA dependent PGE1 infusion were admitted to the neonatal intensive care unit. Eleven (16.7%) had a PDA dependent pulmonary cir-

culation, thirty-one (47%) had a PDA dependent systemic circulation and twenty-four (36.4%) a PDA dependent mixing circulation (Table 1).

Antenatal diagnosis, intervention and perinatal outcomes among infants detected with congenital heart disease are presented in Table 2. Fifty-six infants (84.8%) were followed during pregnancy, thirty-three (50%) were diagnosed antenatally with critical CHD, fifty-seven (83.55%) were born in the tertiary level unit, and nine (13.63%) were transferred from other tertiary level maternities. Thirty-five (53%) infants were born vaginally and thirty-three (47%) by elective caesarean section. There were no significant differences in clinical findings at the onset of disease in the study groups. 60.6% of neonates presented with cyanosis, 74.2% of cases with respiratory distress. Cardiac murmur was present in 100% of newborns with critical CHD.

The mean age of starting PGE1 treatment was 2.06 days with 1.91 (+/-1.44) days for PDA depending pulmonary flow, 2.39 (+/-1.62) days for PDA depending systemic flow and 1.71 (+/-1.12) for PDA depending mixing circulation. The initiation of PEG1 treatment

Table 1. Type of critical congenital heart disease

Disease	number
Heart disease with PDA dependent pulmonary circulation	
Pulmonary atresia/stenosis	8
Complete atrioventricular canal	1
Tetralogy of Fallot with pulmonary atresia	1
Double outlet right ventricle	1
Overall	11
Heart disease with PDA dependent systemic circulation	
Coarctation of the Aorta	18
Complete atrioventricular canal	1
Hypoplastic left ventricle	3
Hypoplastic aortic arch	8
Total anomalous pulmonary venous return	1
Overall	31
Heart disease with PDAdepending mixing circulation	
Transposition of the great artery	24

Table 2. Antenatal diagnosis, intervention and perinatal outcomes among infants detected with congenital heart disease

	PDA dependent Pulmonary circulation N=11	PDA dependent Systemic circulation N= 31	PDA dependent Mixing circulation N=24	Overall N=66	p
Antenatal care	11 (100%)	26 (83.87%)	19 (79.16%)	56 (84.8%)	0.129
Antenatal diagnosis	7 (63.33%)	16(51.61%)	10 (41.66%)	33 (50%)	0.329
Concordance antenatal/postnatal diagnosis	4 (36.36%)	15 (48.38%)	10 (41.66%)	29 (43.9%)	0.586
Birth in the tertiary level care center	3 (27.27%)	2 (6.45%)	5 (20.83%)	9 (13.6%)	0.226
Cesarean section	2 (18.18%)	18 (58.06%)	11 (45.83%)	31 (47%)	0.037
Apgar score less than 7 at 1 minute	2 (18.18%)	2 (6.45%)	3 (12.5%)	7 (10.6%)	0.379
Apgar score less than 7 at 5 minute	0	0	2 (8.33%)	2 (3%)	0.528
Cyanosis	6(54.54%)	13 (41.93%)	21 (87.5%)	40 (60.6%)	0.658
Respiratory distress	7 (63.63%)	19 (61.29%)	23 (95.83%)	49 (74.2%)	0.386
Systolic murmur	11	31	24	66	
Grade I	1(9.09%)	3 (9.67%)	0	4 (6.06%)	
Grade II	4 (36.36%)	9(29.03%)	8 (33.33%)	21 (31.8%)	0.652
Grade III	4 (36.36%)	14 (45.16%)	12 (50%)	30 (45.5%)	
Grade IV	2 (18.18%)	5 (16.12%)	4 (16.66%)	11 (16.7%)	
Echocardiography evaluation, number (SD)	5.27 (±2.1)	6.26 (±3.09)	5.46 (±2.5)	5.8 (±2.7)	0.489

was commenced before 48 hours postpartum in 72%, between 48 to 72 hours in 6%, and after 72 to 120 hours in 21% of neonates detected with PDA dependent circulation (Figure 1). The maxim dose of PEG1 was 0.0378 (+/-0.03) µgrams/kg/minute for PDA depending pulmonary flow group, 0.0521 (+/-0.04) µgrams/kg/minutefor PDA-dependent systemic flow group and 0.050 (+/-0.03) for PDA dependent mixing circulation group ($p<0.05$). PGE1 doses and condition of treatment initiation are shown in Table 3.

PGE1 efficacy

Before PEG1 treatment initiation the mean initial SpO_2 was 77.89 (+/-9.2)% and mean initial oxygen pressure (PO_2) was 26.96 (+/-6.45) mmHg. At the point when the echocardiography indicated a stable open PDA with free blood flow under, the mean SpO_2increased to 89.73 mm Hg and PO_2 rose to 49 mmHg ($p<0.001$). The PGE1 treatment responses are indicated in table 4.

During PGE1 treatment, eleven infants (16.7%) had apnea attacks, five infants (7.5%) had convulsions, thirty-three (50%) had a fever, and forty-seven (71.2%) had leukocytosis (more than 20.000/mm^3), and fifty-two (78.8%) had edema. Other complications possibly related to PGE1 therapy were listed as 25.8% had gastrointestinal intolerance, 45.5% had hypokalemia, and 63.6% had irritability. Additional complications like ectropion, cardiac arrest, and antral hyperplasia were recorded in fewer than 5% of the neonates.

Only one mortality related to PEG1infusion was recorded. A male neonate detected with left ventricle hypoplasia at the five dayspostpartum, died. An initial dose of PEG1, 0.06-0.15 µgrams/kg/minute by continuous infusion had been administered. Table 5 details the side effects during PGE1 infusion.

Echocardiography indicated that all remaining sixty-five newborns had widened PDAs with unrestricted blood flow were bridged to surgical interventions.

Table 3. PGE1 doses, condition of treatment initiation in the study groups

	PDA dependent Pulmonary circulation N=11	PDA dependent Systemic circulation N=31	PDA dependent Mixing circulation N=24	Overall N=66	p
Mean age at PG initiation days (SD)	1.91 (±1.44)	2.39 (±1.62)	1.71 (±1.12)	2.06 (±1.44)	0.709
Initiation PGE1					
0-48 hours	8 (72.7%)	19(61.29%)	21(87.5%)	48 (72.7%)	
48-72 hours	1 (9.09%)	3(9.67%)	0	4 (6.1%)	0.908
72-120 hours	2(18.18%)	9(29.03%)	3 (12.5%)	14 (21.2%)	
Length of PGE1 treatment					
Sum (days)	207	603	384	1194	
Mean (SD)	18.82 (±9.15)	19.45 (±12.69)	16.00 (±9.8)	18.09(±11.15)	0.815
PEG1 initial dose					
µgrams/kg/minute, Mean, (SD)	0.0356 (±0.026)	0.0390 (±0.0398)	0.0429 (±0.027)	0.0398 (±0.033)	0.648
PEG1 minimdose					
µgrams/kg/minute,Mean, (SD)	0.0161 (±0.0119)	0.0167 (±0.0139)	0.0123 (±0.1129)	0.0150 (±0.0126)	0.216
PEG1 maximdose					
µgrams/kg/minute, Mean, (SD)	0.0378 (±0.027)	0.0521 (±0.037)	0.050 (±0.0288)	0.0490 (±0.0329)	0.752

Table 4. PGE1 treatment responses

	PDA dependent Pulmonary circulation N=11	PDA dependent Systemic circulation N= 31	PDA dependent Mixing circulation N=24	Overall N=66	p
FiO2 before PG initiation	40%	35%	37%	36%	0.619
FiO2 after PG initiation	24%	22%	28%	25%	0.788
pO2(mmHg) before PG initiation	26.96	31.26	27.26	29.09	0.418
pO2(mmHg) after PG initiation	39.91	59.01	40.50	49.09	0.200
SpO2(mmHg) before PG initiation	71.55	85.16	71.42	77.89	0.116
SpO2(mmHg) after PG initiation	88.36	92.26	87.08	89.73	0.387

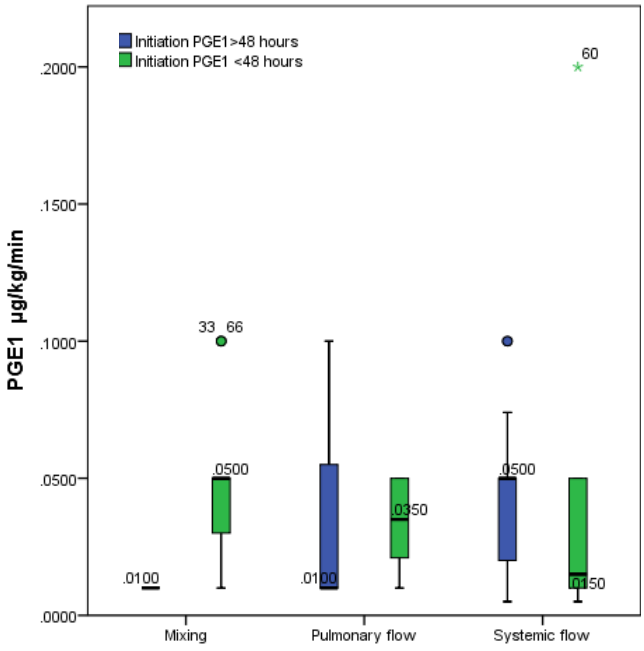

Fig. 1. Level of PGE1initiation dose in accordance with the time of starting infusion and heart defect type

*Boxes are interquartile ranges, the midpoints are medians, whiskers are range and circles are outliers.

Discussion

PGE1 is the currently recommended temporary initial therapy for infants with isolated defects that restrict pulmonary blood flow, poor arterial-venous mixing and conditions that interfere with systemic circulation. This treatment allows the ductus arteriosus to remain patent, maintaining pulmonary and systemic circulation and oxygenation until appropriate surgical intervention can proceed. The policy of administrating PEG1 therapy for neonates with PDA dependent congenital heart disease consisted of an initial dose of PEG1, 0.03-0.05 µgrams/kg/minute. This is a regime suggested by Doblec and should be combined with early a pediatric cardiology consultation, which has been shown to improve outcomes [16].

Yaffe and Aranda suggested that an initial PEG1 infusion of 0.05µgrams/kg/minute may be decreased to 0.01 µgrams/kg/minute for maintenance [17].

In addition to standard parameters like PaO_2 and pulse oximetry, echocardiography was also employed to provide information about the effect of PEG1 on the patency of the ductus arteriosus and on-going monitoring of the size of the PDA allowed PEG1 infusion to be decreased a lower level where stable oxygenation has been achieved. This regime is in accordance with reports which have demonstrated it to be crucial in the management of critical congenital heart disease [18].

When no improvement in oxygenation was obtained after the initial dosage, this increased incrementally by 0.05 µgrams/kg/minute until no further increase of

Table 5. Side effects during PGE1 treatment

	PDA dependent Pulmonary circulation N=11	PDA dependent Systemic circulation N= 31	PDA dependent Mixing circulation N=24	Overall N=66	p
Apnea	2 (18%)	4 (13%)	5 (21%)	11 (16.7%)	0.885
Convulsion	0	2 (6.44%)	3 (13%)	5 (7.5%)	0.301
Irritability	7 (64%)	18 (58.06%)	17(71%)	42 (63.6%)	0.988
Fever	5 (45%)	14 (45%)	14(58%)	33 (50%)	0.746
Gastrointestinal disturbances	1 (9%)	7(23%)	9 (38%)	17 (25.8)	0.171
Antral hyperplasia	0	1(3.22%)	1 (4%)	2 (3%)	0.658
Cardiac arrest	0	2(6%)	0	2 (3%)	0.528
Bradicardia	2 (18%)	5(16%)	6 (25%)	13 (19.7%)	0.892
Leukocytosis	7 (64%)	23 (77%)	16 (67%)	47 (71.2%)	0.550
Hipopotasemia	3 (27%)	16 (51.61%)	11 (46%)	30 (45.5%)	0.190
Edema	9 (82%)	22 (71%)	21 (88%)	52 (78.8%)	0.792
Ectropion	0	1 (3.22%)	1(4%)	2 (3%)	0.528
Hyperextension of the neck	1 (9%)	2 (6.44%)	0	3 (4.5%)	0.436
CRP Mean (SD)	27.72 (62.60)	35.91 (58.93)	12.3 (18.12)	25.96 (49.38)	0.898

oxygenation was needed. This is in accordance with Chamberlin and Lozynski, who state that the ductus arteriosus should be patent within thirty minutes to two hours after the initiation of a continuous infusion of PGE1, who also recommend that it is appropriate to wean the patient off medication after the appropriate level PaO_2 has been achieved [19].

There were numerous reports about the side effects of PEG1 under the current dosage schedule, and it has been demonstrated that side effects increased with increasing dosages [20-23]. In our patients the incidence of the side effects due to PEG1 infusion such as fever, convulsion, apnea and hyperirritability was high compared to Huang et al, this probably being explained by the longer length of PEG1 treatment [24]. This has also been suggested as a cause in other studies, where the same tendencies have been reported when neonates were treated with PEG1 for more than two weeks [25,26].

There were some limitations in the current study which was based solely on the information from chart reviews and record bias may exist. The number of cases was relatively small, but it is considered that the study can provide useful information about perioperative management of neonates with critical congenital heart disease and PDA dependent pulmonary, systemic and mixed blood flow.

Conclusions

For those infants with severe cyanosis or shock caused by PDA dependent heart lesions, initiating and maintaining PGE1 infusion is imperative. The side effects of this beneficial therapy were transient and could be treated.

Conflicts of interest

The authors have nothing to disclose.

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