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ORIGINAL ARTICLE

Long-Term Prostaglandin E1 Infusion for Newborns with Critical Congenital Heart Disease

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Abstract Prostaglandin E1 is crucial for keeping the patent ductus arteriosus in critical congenital heart disease for the survival and palliation of particularly prematurely born babies until a cardiosurgical intervention is available. In this study, the side effects of prostaglandin E1 in newborns with critical congenital heart disease and clinical outcomes were evaluated. Thirty-five newborns diagnosed with critical congenital heart disease were treated with prostaglandin E1 between January 2012 and September 2014 at our hospital. Patient charts were examined for prostaglandin E1 side effects (metabolic, gastric outlet obstruction, apnea), clinical status, and prognosis. Acquired data were analyzed in the SPSS 20.0 program. Patients with birth weight under 2500 g needed more days of prostaglandin E1 infusion than ones with birthweight over 2500 g ($P = 0.016$). The ratio of patients with birth weight under 2500 g who received prostaglandin E1 longer than 7 days was higher than the patients with birth weight over 2500 g ($P = 0.02$). Eighteen side effects were encountered in 11 of 35 patients (31 %). Of these side effects, 1 patient had 4, 4 patients had 2, and 6 patients had only 1 side effect. Discontinuation of the therapy was never needed. Prostaglandin E1 is an accepted therapy modality for survival and outcome in critical congenital heart disease in particularly low-birth-weight babies until a surgical intervention is available. Side effects are not less encountered but are almost always manageable, and discontinuation is not needed.

Keywords Prostaglandin E1 · Newborn · Critical congenital heart disease

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Introduction

Prognosis for critical congenital heart disease (CCHD) has been greatly improved due to pre- and postoperative care by neonatologists and pediatric cardiologists. The preferred medical therapy modality in follow-up of CCHD is prostaglandin E1.

Prostaglandin E1 infusion is crucial in newborns born with ductus-dependant congenital heart disease and is accepted as the mainstay therapy for keeping the patent ductus arteriosus until palliative or corrective surgery. Although applied for short term, occasionally prolonged therapy may be needed particularly in prematurely born babies in order to sustain cardiovascular function until a cardiosurgical intervention occurs [10]. Reported side effects due to long-term infusion include electrolyte imbalance, metabolic alkalosis, hyperostosis, gastric outlet obstruction, and apnea [1, 9]. In the present study, we aimed to evaluate the prostaglandin E1 side effects and clinical outcomes of newborns with CCHD.

Materials and Methods

Between January 2012 and September 2014, 14,307 newborns were born at our hospital, and 4685 newborns were placed in the neonatal intensive care unit. Of all neonates,

35 were diagnosed with ductus-dependant congenital heart disease and were treated with prostaglandin E1. All patients were included in the study, and their charts were examined retrospectively.

Prostaglandin E1 infusion was started and maintained when it proved to be beneficial to the patient and subsequently decreased to the lowest effective dose. Patency of the ductus arteriosus was evaluated with echocardiography on a weekly basis. Infusion was continued until referral to the cardiosurgical intervention.

During the therapy period, the patients' heart rate, respiratory rate, body temperature, blood pressure, and apnea status were monitored. Fluid and electrolyte therapy was maintained for patients according to their daily needs. Biochemical parameters (sodium, potassium, blood urea nitrogen, and creatinine) and blood gas analysis were measured from the blood samples drawn from vein puncture or umbilical catheter on at least a weekly basis. Full enteric feeding was established as soon as possible and closely monitored for gastric outlet obstruction (residual check, vomiting, and abdomen X-ray when needed). Daily urine output was calculated from the patients' diaper weight and recorded on the patients' charts. Hyperostosis was examined with the patients' chest X-rays.

The patients' charts were analyzed and recorded in the SPSS 20.0 program. Patients were grouped according to their birth weight, prostaglandin E1 infusion features, and side effects. Student's *t* test and Fisher's exact test were used in the statistical analysis.

Results

Of the 35 patients, 24 (68 %) were diagnosed prenatally with CCHD by fetal ultrasonography, and 11 (32 %) were diagnosed postnatally by echocardiography for CCHD. In the postnatal cases, a systolic murmur, low hemoglobin saturation values <95 %, or pre- and postductal hemoglobin saturation differences raised suspicion of CCHD, and echocardiography was performed. The distribution of patients according to their CCHD diagnosis is shown in Table 1.

The patients' demographic characteristics and prostaglandin E1 features are shown in Table 2. When compared, patients with birth weight under 2500 g needed more days of prostaglandin E1 infusion than the patients with birth weight over 2500 g ($P = 0.016$). When the two groups were examined separately, the percentage of patients with birth weight under 2500 g who received prostaglandin E1 for longer than 7 days was higher than that of the patients who received <7 days (10 %; $P = 0.02$). Distribution of the patients according to the prostaglandin E1 duration and birth weight, and the negative correlation are shown in Fig. 1 ($R = -0.538$, $P = 0.001$).

Table 1 Congenital cardiac anomalies for prostaglandin E1 infusion

Indication of prostaglandin E1 infusion	Number of patients (%)
Hypoplastic left heart syndrome	10 (26.6)
Pulmonary atresia	5 (14.3)
Pulmonary stenosis	4 (11.4)
Aortic coarctation	4 (11.4)
Transposition of great arteries	2 (5.7)
Aortic hypoplasia	2 (5.7)
Aortic stenosis	1 (2.9)
Fallot's tetralogy	1 (2.9)
Ebstein's anomaly	1 (2.9)
Complex cardiac anomaly	5 (14.3)
Total	35

Eleven of 35 patients (31 %) experienced 18 side effects due to the prostaglandin E1 infusion (Table 3). Of these side effects, 1 patient had 4, 4 patients had 2, and 6 patients had only 1 side effect. All side effects were short-term and manageable. Serum biochemical markers and blood gas analysis of 31 patients were included in the study (four patients had no markers due to short-term prostaglandin E1 use and early surgery). The serum sodium levels of 3 patients were lower than normal levels. This effect was seen at the first week of infusion, and the levels returned to normal later on. Only 1 patient had higher serum potassium levels at the first week but had comorbid kidney issues. The serum blood urea nitrogen and creatinine levels of all patients were normal. Metabolic alkalosis was seen in three patients. This effect was seen in the first week of infusion and continued throughout the second week of infusion in only 1 patient. Gastric outlet obstruction, not due to sepsis or any other causes, was observed in 5 patients. This effect was seen in the first week of infusion in 3 patients and the second week of infusion in 2 patients. Apnea, not due to sepsis or any other cause, was seen in 5 patients. This effect was seen in the first week of infusion in 3 patients, the second week of infusion in 1 patient, and the third week of infusion in 1 patient. One patient showed increased urine output, and other patients showed normal urine output. None of the patients showed hyperostosis, which was documented with the patients' chest X-rays. No statistical significance was found between starting dose, minimum dose, cumulative dose of prostaglandin E1, and the incidence of side effects. Thirty-one patients (88.6 %) underwent surgery, and 4 patients (11.6 %) died before surgery due to complications related to prematurity.

Table 2 Demographic properties and prostaglandin E1 features of patients compared according to birth weight

Features of the patients	BW (g) < 2500 ($n = 9$)	BW (g) > 2500 ($n = 26$)	Overall
Male/female (n)	6/3	14/12	20/15
BW (g) (mean ± SD)	1852 ± 491	3299 ± 397	2927 ± 764
Gestation weeks (mean ± SD)	35.00 ± 3.42	38.42 ± 2.28	37.71 ± 3.00[a]
Starting dose (ng/kg/min) (mean ± SD)	23.57 ± 19.94	53.59 ± 26.72	46.34 ± 3
Minimum dose (ng/kg/min) (mean ± SD)	8.57 ± 2.44	31.36 ± 18.84	25.86 ± 19.13
Cumulative dose (mcg) (mean ± SD)	765.66 ± 565.8	666.23 ± 869.32	691.8 ± 795
Prostaglandin E1 duration (days)	36.56 ± 28.39	7.92 ± 8.83	15.29 ± 20.29[b]
Prostaglandin E1 duration <7 days (n)	2	18	20
Prostaglandin E1 duration >7 days (n)	7	8	15[c]

BW birth weight; *SD* standard deviation; *g* grams

Statistically significant values indicated in Table 2 are as follows: [a] $P = 0.014$ (Student's t test); [b] $P = 0.016$ (Student's t test); [c] $P = 0.02$ (Fisher's exact test)

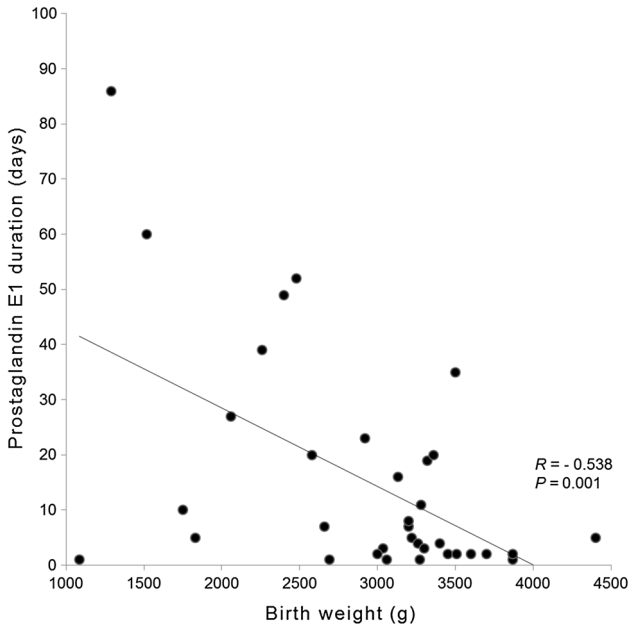

Fig. 1 Prostaglandin E1 duration compared according to birth weight

Table 3 Side effects seen due to prostaglandin E1 infusion

Side effect	Number of patients
Electrolyte imbalance	4
Metabolic alkalosis	3
Gastric outlet obstruction	5
Apnea	5
Increased urine output	1
Hyperostosis	–
Total	18

Discussion

In this study, important outcomes were achieved related to prostaglandin E1 use in babies born with CCHD. Longer duration of prostaglandin E1 infusion is required in prematurely born babies with CCHD. Prostaglandin E1-dependant side effects are not less often encountered and can be seen even in early stages of therapy but almost always are short-term and manageable, and discontinuation is not needed. Newborns with CCHD, particularly premature newborns, can be kept alive until the cardiovascular structures reach a desirable size for surgical intervention [2]. The patients in our study needed an extended period of time for medical palliation with prostaglandin E1 before palliative or corrective surgery due to various reasons: increased risk of mortality and morbidity in neonates (particularly those born preterm or with low birth weight), our institution's experience and preferences, technical limitations in small infants, and patients' specific conditions.

Flow through the ductus arteriosus is vital even from the first hours of life and later on in CCHD with decreased pulmonary flow, decreased systemic flow, and nonmixing syndromes of oxygenized blood with venous blood. In such circumstances, shunting through the ductus arteriosus is needed for palliation and patient survival. Surgical shunting is almost impossible and has high mortality rates because of the small cardiovascular structures. Prostaglandin E1 infusion maintains ductal patency, performs a medical palliative shunt, and gains time particularly in preterm babies with operable CCHD until the cardiosurgical intervention is achieved [1, 3, 9]. Most of our patients (88.6 %) underwent a surgical intervention due to use of prostaglandin E1 infusion such as Norwood stage 1 and modified BT shunting.

Many reports have been published about the dosing and side effects of the drug. The accepted recommendation is an initial dose of 100–50 ng/kg/min and titration down depending on the patient's clinical status [3]. Despite current practice, lower initial (20 ng/kg/min) doses are reported to be safe and have a good response to therapy [5]. In our practice, the mean initial doses were between two regimens (46.34 ± 3 ng/kg/min). Metabolic side effects and gastric outlet obstruction are generally reported in later stages of the therapy with a longer duration of infusion [1, 3, 8, 9]. We observed that these side effects can be encountered even during the first week of infusion. We did not find a statistical significance between dosing of prostaglandin E1 and these side effects. We assumed that the absence of significance might be related to low number of study group. On the other hand, incidence of apnea is noted in approximately 12 %, generally in early stages of therapy particularly in low-birth-weight babies [1, 4, 6, 7]. The incidence and timing of apnea were similar in our study. Various studies have reported that prostaglandin E1-dependant side effects generally needed no comprehensive intervention, and discontinuation of the therapy is generally not needed [1, 3–9]. In our practice, all side effects were manageable, and therapy was not discontinued due to side effects.

In conclusion, prostaglandin E1 in CCHD is an important therapy option particularly for prematurely born babies to provide a medical palliative shunt until an interventional procedure is available. We believe that prostaglandin E1 is safe and has manageable side effects even in long-term infusion.

Compliance with Ethical Standards

Conflict of interest None.

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