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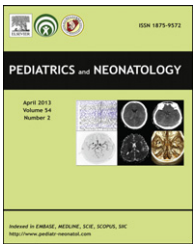

ORIGINAL ARTICLE

Reappraisal of the Prostaglandin E1 Dose for Early Newborns with Patent Ductus Arteriosus-Dependent Pulmonary Circulation

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Key Words
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Objectives: The usual initial dose of prostaglandin E1 (PGE1) for ductal-dependent congenital heart disease (CHD) is 50–100 ng/kg/minute. The aim of this study was to review our experience of a low initial dose of PGE1 treatment in early newborns with congenital heart disease and patent ductus arteriosus (PDA)-dependent pulmonary flow.
Methods: We reviewed the clinical data of 33 newborns with CHD and PDA-dependent pulmonary circulation who were admitted from January 2005 to December 2010. Clinical parameters were collected, including, PGE1 dosage, oxygenation condition, vital signs, and other related clinical parameters during admission. Echocardiography was employed to assess the status of the PDA as clinically indicated.
Results: Thirty-three newborns, including 17 males and 16 females, with CHD and PDA-dependent pulmonary circulation were enrolled in the study. Their mean age was 2.9 ± 5.1 (within the range of 1–26) days with a median of 1.0 day. Among the 33 cases, 25 were diagnosed with pulmonary atresia and eight with critical pulmonary stenosis. Twenty-five of our patients were treated with the initial low-dosage regimen of 20.0 ± 7.4 ng/kg/minute in our neonatal intensive care unit. None of these 25 patients with had significant apnea necessitating intubation and none had hypotension, fever, convulsion or cortical hyperostosis. Three of the eight patients who were treated with high-dose PGE1 (39 ± 13.2 ng/kg/minute) before referral to our unit had apnea and intubation after PGE1 use. All patients had adequate PDA patency with a low maintenance dose of 10.5 ± 5.3 ng/kg/minute before operation under our protocol.

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Conclusion: In our experience, adequate PDA flows in early newborns with CHD and PDA-dependent pulmonary circulation could be achieved at a much lower dose than recommended in the literature. The lower dose of PGE1 also causes much fewer complications, such as apnea, fever, and hypotension. For early newborns with CHD and PDA-dependent pulmonary circulation, treatment with a lower initial dose of PGE1 of 20 ng/kg/minute and a maintenance dose of 10 ng/kg/minute is recommended.

1. Introduction

Ductus arteriosus is a vessel vital for the fetal circulation[1] that becomes unnecessary and usually closes within days after birth.[2–4] However, some infants with congenital heart disease (CHD) rely on ductus arteriosus.[5,6] To prevent the patent ductus arteriosus (PDA) closure after birth, prostaglandin E1 (PGE1) has been routinely used for these patients in intensive care units for more than 30 years.[7]

According to the literature, the usual initial dose of PGE1 is around 50–100 ng/kg/minute to keep the ductus arteriosus open[8–13]; however, such a high initial PGE1 dose often results in side effects, such as fever, respiratory distress, diarrhea, and apnea.[14–16] To avoid these complications, we have titrated the PGE1 to a lower-dose regimen for more than a decade. The purpose of this study was to evaluate the application of the lower dose of PGE1 in newborns with CHD and PDA-dependent pulmonary circulation.

2. Materials and Methods

Our policy of administrating PGE1 therapy for newborns with PDA-dependent CHD is that in the situation of aggravating cyanosis compatible with impending closure in the neonatal intensive care unit, an initial dose of 20 ng/kg/minute of PGE1 is started. If there is no improvement in oxygenation, stepwise dose increases of 5 ng/kg/minute are administered until no further increase of oxygenation occurs, or until pulse oximetry (SpO_2) has reached the pre-closure level of the ductus arteriosus. After stabilization for about 1 day, the initial dose is gradually tapered to around 10 ng/kg/minute as maintenance to keep the PDA open.

We reviewed the clinical records of 33 newborns with CHD with PDA-dependent pulmonary circulations who were admitted to our hospital between January 2005 and December 2010. We defined an intravenous dose of <30 ng/kg/minute of PGE1 for initial re-opening of the PDA as low dose, and a dose >30 ng/kg/minute as high-dose. We analyzed the dose of PGE1, blood gas data (from umbilical vein, central venous catheter or peripheral central venous catheter, depending on the availability of the line), vital signs, and their complications, etc. Echocardiography was performed to assess the status and diameter of the PDA. Continuous parameters were compared using the two-tailed independent Student *t* test. Analyses of significance were performed. A *p* value of <0.05 was considered to be statistically significant.

3. Results

During the study period, 33 newborns with CHD with PDA-dependent pulmonary circulation were admitted to our neonatal intensive care unit. The various congenital cardiac defects of ductus-dependent pulmonary circulation are shown in Table 1. Among the 33 newborns, 16 (48%) were females and 17 (52%) were males. Twenty-five patients (75%) had pulmonary atresia and the other eight patients (25%) had pulmonary stenosis. The mean gestational age was 37 ± 2 weeks and the mean birth body weight was 2827 ± 521 g. The mean age on starting PGE1 treatment was at 3.3 ± 5.8 (within the range of 1–26) days of age, with a median of 1.0 day.

The initial lower-PGE1-dose regimen of 20.0 ± 7.4 ng/kg/minute (in the range of 10–30 ng/kg/minute) was used in 25 patients whose intravenous PGE1 therapy started in our neonatal intensive care unit. Before treatment, the mean diameter of ductus arteriosus was 1.7 ± 0.3 mm, as measured by echocardiography. After treatment, the mean ductus arteriosus diameter improved to 3.7 ± 0.7 mm.

When the PDA was wide open, we gradually tapered the mean maintenance dosage to 10.5 ± 5.3 (within the range of 5–20) ng/kg/minute. Their mean initial SpO_2 was

Table 1 Type of coronary heart disease among the patients.

Disease	Number
PA + TOF	8
TOF + PS	3
PA + IVS	5
Critical PS	2
PA + CAVC	3
PA + CAVC + TAPVR	2
PA + DORV	2
PS + CAVC + DORV	2
TOF + PA + VSD	2
PA + SV	2
PA + TA	1
Critical PS + VSD	1
Total	33

ASD = atrial septal defect; CAVC = complete atrioventricular canal; DORV = double outlet right ventricle; IVS = intact ventricular septum; PA = pulmonary atresia; PS = pulmonary stenosis; SV = single ventricle; TA = tricuspid atresia; TAPVR = total anomalous pulmonary venous return; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

69 ± 9% and mean initial venous oxygen pressure (PO_2) was 26.48 ± 6.45 mmHg. At the point when stable wide open PDA (diameter of ductus arteriosus widens with unrestricted blood flow under echocardiography) was achieved, their mean SpO_2 increased to 85.33 ± 7.92% ($p < 0.05$) and mean venous PO_2 of central vein blood gas increased to 40.85 ± 9.56 mmHg, both with statistical significance (Table 2).

For the other eight patients, an initial high dose regimen of 39 ± 13.2 (within the range of 30—70) ng/kg/minute was employed. All eight patients had been transferred from other hospitals and received PGE1 starting at 1.5 ± 0.9 (within the range of 1—3) days of age with a median of 1.0 day before referral. There was no statistically significant difference in age at starting PGE1 treatment between the initial low- and high-dose groups.

Parameters such as vital signs, oxygen saturation, oxygen concentration in blood gas and general activity were monitored serially. During PGE1 treatment, eight of the 33 newborns (24%) had apnea attacks. Among them, five newborns were treated with low initial dose and three newborns were treated with high initial dose before arrival. Compared to the 25 patients receiving low initial PGE1 dosage who did not need intubation, three of the eight newborns (37.5%) receiving a high initial PGE1 dosage needed intubation before arrival from other hospitals due to an unstable respiratory pattern. Concerning other complications possibly related to PGE1 therapy, loose stool occurred in two newborns (one in the high- and another in the low-dose group). None of the 33 patients had other complications such as fever, convulsion, or hypotension, etc. (Table 3).

The only mortality before operation was one male newborn who was born at gestational age of 40+ weeks, with a birth body weight 2830 g and *situs inversus*, dextrocardia, common atrial-ventricular canal, pulmonary atresia, severe atrioventricular valve regurgitation and large PDA. He was initially administered 6—12 ng/kg/minute of PGE1 under continuous infusion. Severe heart failure due to atrioventricular valve regurgitation occurred at 3 days of age. Emergent endotracheal tube intubation was performed and large-dose inotropic agents were given. His general condition deteriorated with severe metabolic acidosis and desaturation with SpO_2 of <70%, even under ventilator support with FiO_2 at 100%. The parents hesitated over consenting to surgical repair and the baby expired 26 days after admission. Throughout the course the PDA was wide open at a low maintenance dose. It is clear that the severe atrioventricular valve regurgitation contributed to the severe desaturation of the patient.

Table 2 PGE1 dosage and treatment responses.

	Initial	Maintain	p^*
PGE1 (ng/kg/minute)	20.02 ± 7.4	10.54 ± 5.27	—
PO_2 (mmHg)	26.48 ± 6.45	40.85 ± 9.56	<0.001
SpO_2 (%)	69.32 ± 9.01	85.33 ± 7.92	<0.001

*$p < 0.05$ if compared with normal population by WHO standard. PGE1 = prostaglandin E-1; PO_2 = pressure of oxygen from central vein blood gas.

Table 3 Side effects during lower-dose PGE1 treatment of 33 patients.

Symptoms	Numbers (%)
Apnea	8 (24)
Intubation due to apnea	0 (0)
Fever	0 (0)
Convulsion	0 (0)
Hypotension	0 (0)
Cortical hyperostosis	0 (0)
Loose stool	2 (6)
Hemorrhagic diathesis	0 (0)

Except for the newborn (3%) who had been transferred from another hospital and expired as described above, there were no mortalities related to PGE1 use in our series. All the other 32 newborns had stable opening PDA and bridged smoothly to surgical intervention.

4. Discussion

PGE1 was first noted as a potent relaxant of the ductus arteriosus in 1973 and it has been used to keep the ductus arteriosus open for decades.[17] It was approved in 1981 by the Food and Drug Administration (FDA) in the United States. There were numerous reports about its side effects under the current dosage schedule,[7,9—12,17] such as apnea, fever, hypotension, and diarrhea which increased with increasing dosages of PGE1.[14,15,18—23]

As mentioned above, higher PGE1 dosages cause many complications. However, the current recommended dose for PGE1 use has remained at 50—100 ng/kg/minute, and surprisingly there has been no change in this dose recommendation since its first introduction into clinical use.[8,10—14] We have titrated the dosage in our neonatal intensive care unit for over a decade with an initial dosage at around 20 ng/kg/minute and a maintenance dosage of around 10 ng/kg/minute. In addition to the conventional clinical parameters, we also used echocardiography to provide useful information about the effect of PGE1 on the patency of the ductus arteriosus. Our patients showed a universally good response to low-dose PGE1 infusion. Our experience also showed that the initial low PGE1 dose could be further tapered down to around 10 ng/kg/minute once a stable oxygenation condition has been achieved.

In our patients, the PO_2 data was obtained from central vein gas (umbilical vein or central vein) because this is safe and convenient for newborn patients. It was very difficult to set up an arterial line under unstable conditions and some reports had supported the assertion that central venous blood gas values may be an acceptable way to provide the information.[24,25] Despite this, the venous PO_2 also improved significantly under lower initial PGE1 dose.

The dosage of PGE1 and duration of its use are considered to relate to the side effects.[22,26] In our patients given a lower initial dosage, the incidences of side effects due to PGE1 (such as apnea, fever, convulsion, hypotension and diarrhea) were all lower than the reported series.[14,20—23,27—30] In particular, only five newborns (20%) given the lower initial PGE1 dose had apnea attacks; all the apnea attacks

were transient and could be treated with aminophilline, with none needing intubation. This was less than the three newborns who were initially given a high initial dose at the referral hospital (37.5%). Since apnea is an important complication related to PGE1 use, our low dose of PGE1 appears very beneficial.

Kramer et al.[29] suggested that a low dose of PGE1 infusion at an initial dose of <10 ng/kg/minute could result in less apnea. However, in the patient group, very few (12/91) patients were given a initial dose of PGE1 of <20 ng/kg/minute, which means that a small percentage of patients could have their PDA open with PGE at a dose of <20 ng/kg/minute. Our past experience showed the same tendency and thus we chose the initial dose of 20 ng/kg/minute of PGE1 as our low-dose policy.

In our experience, the duration of PGE1 treatment before the cardiac surgery was 11.24 ± 6.24 days. If newborns were treated with PGE1 for longer than 2 weeks, fluid electrolyte, digestion and other clinical conditions should be monitored closely.[22,23,26] Recently, there have been reports of stent implantation in the ductus arteriosus for pulmonary or systemic circulation.[31–33] However, the morphology of the ductus arteriosus, clinical conditions and operators' experiences influence the outcome of the procedures.[33] Before the Blalock-Taussig shunt or other corrective operation on these newborns,[34–37] PGE1 treatment is still a reliable method for short-term bridging before surgery.

5. Study Limitations

There were some limitations in our study. It was based solely on the information from chart reviews and some record bias exists in the results. The number of cases was relatively small. However, due to the declining birthrate in Taiwan,[6] large case series are a challenge. The mean age of initial PGE1 dose was also <2 weeks (median 1 day), both in the high- and low-dose groups. Thus, bias may exist regarding the effects on those older newborns. We believe our unique experience can provide useful information about a low initial dose of PGE1 in early newborns with CHD and ductus-dependent pulmonary blood flow.

6. Conclusion

Careful titration with a lower initial dose of 20 ng/kg/minute rather than 100 ng/kg/minute or 50–100 ng/kg/minute[7–9,12] and rapid tapering to a maintenance dosage of PGE1 at 10 ng/kg/minute is effective to keep the ductus arteriosus open, with fewer side effects.[7–9,12] Our low initial dose is only 25–50% of the conventional dose. We expect wide application of low-dose PGE1 in early newborns with critical CHD and PDA-dependent pulmonary circulation in the future. An additional study is now being undertaken to enroll more cases of various critical CHDs with ductal-dependent systemic circulation.

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