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ORIGINAL ARTICLE

Do Predictors Exist for a Successful Withdrawal of Preoperative Prostaglandin E_1 from Neonates with d-Transposition of the Great Arteries and Intact Ventricular Septum?

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Abstract Prostaglandin E_1 (PGE_1) is given to neonates with d-transposition of the great arteries (d-TGA) to reduce cyanosis by reopening and maintaining the patency of the ductus arteriosus. To avoid side effects, this medication can be stopped for hemodynamically stable patients after balloon atrial septostomy (BAS). A consecutive series of neonates with d-TGA and an intact ventricular septum (IVS) presenting from 2000 through 2005 was analyzed retrospectively to search for side effects of PGE_1 and to identify predictors for a safe preoperative withdrawal. The medication was stopped for hemodynamically stable patients with transcutaneous oxygen saturations higher than 80% after BAS and reinitiated for patients with an oxygen saturation lower than 65%. Patients successfully weaned were compared with those who had failed weaning in terms of atrial septal defect (ASD) size, ductus arteriosus size, and the transcutaneous oxygen saturation. Prostaglandin E_1 was initiated for all 43 neonates with d-TGA. The median maintenance dose of PGE_1 was 0.00625 μg/kg/min (range, 0.00313–0.050 μg/kg/min) for a median duration of 6 days (range, 1–12 days). For 16 patients, PGE_1 was preoperatively withdrawn but then had to be reinitiated for 7 of the 16 patients. No predictors for a successful weaning of PGE_1 were found based on ASD size, ductus arteriosus size, or oxygen saturation. The adverse effects of PGE_1 were apnea in 10 patients and fever in 19 patients. Neither seizures nor necrotizing enterocolitis was documented. Prostaglandin E_1 was successfully withdrawn for a minority of hemodynamically stable patients with d-TGA. No predictors for a successful weaning could be identified. Because apnea and fever are common side effects, withdrawal of PGE_1 after BAS may improve patient safety and comfort. In this patient group, if PGE_1 withdrawal was not well tolerated, it could be safely reinitiated. There were no serious side effects of PGE_1.

Keywords D-transposition of the great arteries · Neonates · Preoperative management · Prostaglandin E_1

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Prostaglandin E_1 (PGE_1) is a potent vasodilator for reopening and maintaining the patency of the ductus arteriosus [5]. Intravenous PGE_1 is the standard of care for the early stabilization of neonates with profound hypoxemia and suspected ductus dependent cyanotic congenital heart defect. Although the administration of PGE_1 can be lifesaving for neonates with a ductus-dependent physiology, it has the potential for serious side effects [3, 7, 11]. Prostaglandin E_1 causes peripheral vasodilation in the pulmonary and systemic circulations, with the possibility of cutaneous flushing and clinically relevant hypotension. The cerebral side effects of PGE_1 can result in jitteriness, elevated body temperature, apnea, and seizure-like activities.

In addition, PGE_1 is known to affect the gastrointestinal tract and can cause necrotizing enterocolitis. Abnormal texture with edema and increased friability of the ductal tissue and adjacent vessels has been noted at the time of

surgery in patients after preoperative treatment with PGE_1. The histopathologic correlates are edema and hemorrhage of the vessel media [4]. For the administration of PGE_1, a reliable intravenous line is required, with the potential risk of catheter-related sepsis.

As soon as the diagnosis is suspected, neonates with d-TGA and intact ventricular septum (IVS) are routinely administered PGE_1 to reopen the ductus arteriosus or to maintain its patency and hence improve mixing of oxygenated and deoxygenated blood, with increased systemic oxygenation before corrective surgery [10, 12]. A balloon atrial septostomy (BAS) needs to be performed if there is inadequate mixing at the atrial level [1]. After this intervention, PGE_1 can be weaned for some patients without any adverse events. However, the optimal timing for discontinuation of PGE_1 and predictors for a successful withdrawal remain unclear. It also is not known whether the risk for potential cardiac collapse after PGE_1 withdrawal outweighs the risk for potential PGE_1 side effects in the contemporary approach to an early arterial switch operation.

We therefore conducted a retrospective analysis of preoperative PGE_1 administration for neonates with d-TGA and IVS to define a subgroup of patients from whom PGE_1 may be safely withdrawn.

Methods

This study was a retrospective analysis at a single tertiary referral pediatric center. All consecutive neonates with d-TGA and IVS admitted to our pediatric cardiac intensive care unit (PICU) from January 2000 until September 2005 were included in the study. Patients with additional cardiac malformations were excluded, but those with small ventricular septal defects (<2 mm) were enrolled.

For the neonates with clinically suspected d-TGA and IVS or an emergency echocardiographic diagnosis in the birth clinic, PGE_1 was administered immediately at a dosage of 0.1 μg/kg/min to reopen the ductus arteriosus. At the same time, a dopamine infusion of 4 μg/kg/min was initiated, if necessary, to prevent severe hypotension from PGE_1 due to systemic vasodilation. The patients then were nasotracheally intubated and transported to the intensive care unit (ICU). The referring birth clinics are relatively nearby, with a maximum transport duration of 2 h. Some patients with stable hemodynamics facing a very short transport distance were transferred while breathing spontaneously.

At arrival in the intensive care unit, a BAS was performed if the interatrial communication was deemed too small (<5 mm) for adequate mixing of oxygenated and deoxygenated blood, as judged by echocardiography. The preferred access to BAS was the umbilical vein. In case of failure, a femoral vein was used.

With a satisfactory rise in oxygen saturation and hemodynamic stability, PGE_1 was progressively tapered down in 50% increments within 2 to 4 h and again after 4 to 8 h to a minimal dosage of 0.00625 μg/kg/min. The PGE_1 was stopped if the patient remained stable according to individual clinical judgment and if the patient's transcutaneous oxygen saturation remained above 80%.

For deteriorating patients, PGE_1 infusion was reinitiated if the saturation dropped and remained below 65% or if there was an increase in lactate acidosis. Cautious enteral feeding was initiated for each patient as soon as possible. Heart rate, respiratory rate, oxygen saturation, blood pressure, and body temperature were regularly monitored.

We reviewed hospital charts, nursing notes, and echocardiographic reports or stored echocardiographic studies where indicated. Size of the ASD, size of the ductus arteriosus as measured by transthoracic echocardiography, and transcutaneous saturation were suspected to be predictors for a successful weaning from PGE_1. The size of the ASD was obtained after BAS by measuring the largest diameter of the interatrial communication in the subcostal view. The size of the ductus arteriosus was measured as the smallest diameter of the duct obtained from a modified parasternal view.

All measurements were taken from two-dimensional cross-sectional echocardiography images obtained using a 12-MHz transducer (Sonos 5500, Philips Healthcare, Best, NL). Ductus arteriosus size was measured at the time of diagnosis and at further follow-up assessments depending on the clinical condition. An immediate preoperative echo scan was not routinely obtained. The mean transcutaneous oxygen saturation was documented the first 8 h after BAS.

Possible complications of PGE_1 were recorded as follows. Apneas were classified as mild or severe depending on the need for intubation and ventilation. The need for intubation was judged individually by the ICU team depending on the severity of the neonate's impaired general condition, the neonate's hemodynamic state, and the signs of respiratory failure (i.e., hypoxemia or hypercarbia).

Extubation was performed if the patient was awake and showed appropriate behaviour, if adequate leak around the endotracheal tube was observed, if no signs of distress were detected during assisted spontaneous breathing with a fraction of inspired oxygen less than 0.4, and if the patient remained normocapnic during the weaning process. Fever was noted if the body temperature exceeded 38°C. Seizures were judged by clinical observation. Mean arterial blood pressure below the age-specific limits, obtained by noninvasive measurement, was defined as hypotension. Irritability, trembling, or diarrhea also was documented.

For statistical analysis, the patients whose PGE_1 was withdrawn were divided into two groups: "group success" with successful PGE_1 weaning and "group failure" with failed PGE_1 discontinuation. The study was approved by the local ethics committee, and written informed consent was obtained from the parents or legal guardians for the data collection.

Statistical Analysis

Measurements are presented as median and range. Patient groups were compared using the Student's *t*-test and the chi-square test where appropriate. A significant difference was defined as a *p* value less than 0.05. Data were analyzed using the statistical software SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The study population consisted of 43 patients (30 boys and 13 girls). Their median birth weight was 3,400 g (range, 1,900–4,660 g), and their median gestational age was 39.9 weeks (range, 35.1–41.7 weeks). For all 43 patients, continuous application of PGE_1 was initiated intravenously. A prenatal diagnosis was available for three patients, so continuous PGE_1 administration was initiated shortly after their birth. For 40 patients, PGE_1 was initiated on clinical suspicion at a median time of 5 h (range, 2–110 h) after birth. A loading dose of 0.1 μg/kg/min was given to 23 patients. The median maintenance dose of 0.00625 μg/kg/min (range, 0.00313–0.050 μg/kg/min) given for a median duration of 6 days (range, 1–12 days).

Mechanical ventilation was initiated primarily for resuscitation or safety during transfer of 41 patients for a median duration of 3 days (range, 1–8 days). At arrival in our PICU, BAS was performed for 40 patients with a restrictive ASD at a median time of 9 h (range, 2–120 h) after birth. The median ASD size after BAS was 6 mm (range, 3.5–9 mm).

Vascular access was via the umbilical vein in 18 of 40 patients and via the femoral vein in 18 patients. For four patients, information regarding vascular access was missing. The median oxygen saturation before BAS was 70% (range, 40–85%) and increased to 80% (range, 40–90%) 1 day after BAS.

For 16 patients, PGE_1 was gradually withdrawn within a median time of 5 days (range, 1–12 days). This preoperative strategy was successful for nine patients ("group success") who remained stable without any further PGE_1 administration until corrective surgery was performed. However, PGE_1 had to be reinitiated in seven patients for severe cyanosis ("group failure") (Fig. 1). The cessation of PGE_1 could not be predicted by size of the ASD after BAS, size of the ductus arteriosus, or transcutaneous oxygen saturation (Table 1).

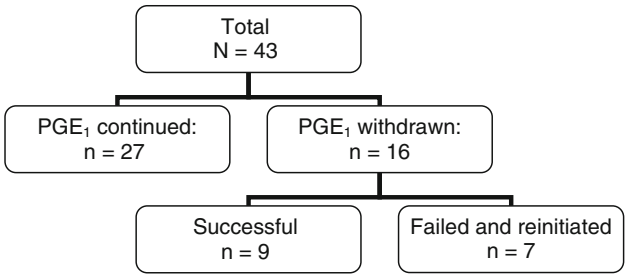

Fig. 1 Number of observed patients with transposition of the great arteries (TGA) and intact ventricular septum (IVS), prostaglandin E_1 (PGE_1) management, and outcome

Table 1 Analysis of patients whose prostaglandin E_1 (PGE_1) was withdrawn: comparison of "group success" versus "group failure" in terms of demographic data and possible predictors

	Group success: PGE_1 withdrawal successful *n* (range)	Group failure: PGE_1 withdrawal failed *n* (range)	*p* value
No. of patients	9	7	
Gestational age (weeks)	38.7 (35.1–40.7)	39.9 (36.9–41.1)	0.57
Weight at birth (kg)	3.2 (1.9–3.8)	3.7 (2.6–4.7)	0.12
Apgar at 5 min	8 (8–10)	9 (7–10)	0.74
Antenatal diagnosis	2	0	0.20
Age at diagnosis (h)	9 (2–43)	11 (3–120)	0.30
Ductus arteriosus size (mm)[a]	3.5 (3–5)	4 (2.8–6)	0.78
ASD size (mm)[b]	6 (4–9)	5.5 (3.5–7.5)	0.40
SO_2 before BAS (%)	75 (60–85)	70 (50–80)	0.28
SO_2 1 day after BAS (%)	85 (75–90)	80 (70–85)	0.14

Values are given as *n* or as median (range) respectively

[a] Ductus arteriosus size: smallest diameter of the ductus arteriosus as measured by echocardiogaphy on the day of BAS

[b] ASD size: largest diameter of the ASD immediately after BAS

ASD atrial septal defect, *SO_2* oxygen saturation, *BAS* balloon atrial septostomy

For 15 hemodynamically unstable patients, catecholamins (dobutamine, epinephrine, and norepinephrine) were administered at a low dosage. Antibiotic therapy was initiated at birth for 18 of the 43 patients, and discontinued for all the patients after 48 h when negative blood cultures were obtained.

Major complications of PGE_1 such as apnea requiring reintubation, necrotizing enterocolitis, or convulsions were not observed in our study population. For 10 of the 43 patients, milder apnea occurred. After BAS, a low dosage

of inotropic drugs was necessary for 19 of the patients still receiving PGE_1. Fever was reported for 19 of the patients as a possible side effect of PGE_1. Irritability was documented in 9 of the patients.

The arterial switch operation was performed at a median age of 7 days (range, 4–13 days). All the patients went to the operating room in a stable condition. None of the operations were complicated by tissue fragility or swelling, as observed intraoperatively by the surgeons.

Discussion

In different centers, large variations in the protocol for PGE_1 administration and timing of surgery for d-TGA can be found. At the same time, few data are published regarding the optimal timing of potential PGE_1 cessation. In the first part of this study, we focused on a group of neonates with d-TGA after successful BAS with adequate interatrial mixing whose PGE_1 could safely be withdrawn before surgery. The results of our study suggest that failure of weaning from PGE_1 cannot be properly estimated beforehand by clinical or echocardiographic data.

After cessation of PGE_1, the ductus arteriosus constricts and eventually closes spontaneously. Therefore, the mixing of oxygenated and deoxygenated blood will decrease at the level of the ductus arteriosus and be limited to the interatrial mixing. In this situation, the amount of shunted blood is determined by the size of the ASD and the atrial filling pressures, which again depend primarily on ventricular performance, heart rate, and peripheral vascular resistances of the systemic and pulmonary circulations. In hemodynamically stable patients with d-TGA and IVS, the size of the ASD could therefore be a fairly good predictor of interatrial mixing. However, the atrial filling pressures and its determinants were not taken into account in this retrospective study.

The most striking hemodynamic change within the first days of life is the natural fall in pulmonary vascular resistance during the physiologic process of transitional circulation. This process can be rapidly fluctuating, particularly in sick neonates after sustained postnatal hypoxemia. Prostaglandin E_1, known to be a potent pulmonary vasodilator [2, 5], will therefore contribute to an increased pulmonary blood flow and an overall more stable hemodynamic condition. At discontinuation of PGE_1, the initial pulmonary vasoconstricion may reappear and increase right-to-left shunting at the ductus arteriosus and ASD levels.

In a population of 45 neonates with d-TGA and IVS, Finan et al. [3] reported a significantly higher incidence of rebound hypoxemia at aggressive discontinuation of the PGE_1 infusion after BAS. This clinical observation was attributed to the changes in pulmonary vascular resistance by PGE_1. It is probable that in the "group success" of our study with achieved cessation of PGE_1, the pulmonary vascular resistance had already decreased, enabling increased pulmonary blood flow. On the other hand, in the "group failure," increased pulmonary vascular resistance may have persisted and prevented the cessation of PGE_1 despite adequate mixing of oxygenated and deoxygenated blood.

Retrospectively, we cannot evaluate whether the rebound hypoxemia after cessation of PGE_1 was due to ductus arteriosus closure or increased pulmonary vascular resistance. The retrospective design of this study prohibited a direct measurement of the pulmonary vascular resistance. Furthermore, the residual shunting at the level of the ductus arteriosus cannot be properly estimated due to the complexity of the process of dilation and constriction of the ductus arteriosus.

In the second part of the study, we focused on side effects of PGE_1 in the whole study population of 43 patients. Significant side effects of PGE_1 are reported to occur in 23% to 50% of patients with congenital heart defect [8]. In our study population, severe side effects (i.e., seizure-like episodes and necrotizing enterocolitis) were not observed. When various studies of PGE_1 side effects are compared, the findings seem to indicate that serious adverse events are limited to at-risk populations and to patients who require high maintenance doses of PGE [8, 9]. Our study did not include patients with additional risk factors, and the maintenance dose of PGE_1 was kept low.

In our study population, an involvement of the central nervous system was frequently observed. A certain amount of jitteriness and hyperreactivity was noted in most of the neonates receiving PGE_1, although this was difficult to quantify retrospectively. Seizures did not occur. In the study of Lewis et al. [7], central nervous system events were observed more often in acidotic patients and in those with a longer duration of PGE_1 infusion. The highest incidence of seizure-like activities was noted in the study of Ohara et al. [9], but it is not obvious from this study whether these patients had additional risk factors such as asphyxia or prematurity.

The highest incidence of necrotizing enterocolitis was reported by Singh et al. [11]. In their study, 7 of 34 patients treated with PGE_1 were affected. Four of these seven patients were found in the high-risk population of premature neonates.

Our incidence of apnea was within the range of other reports [7–9, 11], and mechanical ventilation for prolonged apnea was not necessary for any of our patients. One-fourth of all neonates to whom PGE_1 is administered will experience apnea, highlighting the need for close cardiopulmonary monitoring of these patients in an intensive care, intermediate care, or neonatal unit.

Notably, none of our study patients had tissue alterations (i.e., swelling and tissue fragility) at the time of surgery, which could complicate surgical repair. This side effect has been reported in older studies, in which PGE_1 was administered over a longer period [4, 6]. Reducing the exposure to PGE_1 not only by earlier surgical correction but also by a lowered dosage as we aimed to achieve for our patient population may have contributed to our surgeons' subjective impression of normal tissue handling during the arterial switch operation, although our study had neither a control group nor histopathologic findings.

Our study is limited by the fact that the subgroups of patients whose PGE_1 was withdrawn are too small to show a significant difference in the statistical analysis. Furthermore, the impact of PGE_1 on pulmonary vascular resistance remains speculative because a direct measurement of pulmonary artery pressure and flow was not obtained.

Conclusions

To improve patient comfort and to reduce potential PGE_1-related morbidity, an effort should be made to withdraw PGE_1 preoperatively in stable neonates with d-TGA after BAS. Patients should be monitored closely thereafter because the resulting hemodynamic course cannot be predicted from the ASD size, ductus arteriosus size, or oxygen saturation after BAS. In case of rebound hypoxemia in our study, PGE_1 could be safely reinitiated in this small patient group and had minimal side effects with low-dose administration.

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