Safety and Tolerance of Prostaglandin E1 Therapy in Neonates with Duct-Dependent Congenital Heart Disease: A 10-Year Retrospective Study

Abdelmoula. S [(1)], El Ouaer. M [(1)], El Ghali. M [(1)], Ben Rhaiem. M [(1)], Bizid.M [(1)], Chamtouri.I [(2)], Ben Hamida. H [(1)]

[(1)] Department of Intensive Care and Neonatal Medicine , University Hospital of Monastir, Tunisia
[(2)] Department of cardiology B , University Hospital of Monastir, Tunisia

ABSTRACT

Introduction: Congenital heart diseases (CHD) are the most common birth defects. Duct-dependent lesions require prostaglandin E1 (PGE1) to maintain ductus arteriosus patency. While life-saving, PGE1 is associated with significant side effects. This study aimed to evaluate the safety and tolerance profile of PGE1 therapy in neonates with ductal-dependent CHD in a real-life neonatal intensive care setting.

Methods: A retrospective, descriptive, single-center study was conducted, including 63 newborns with duct-dependent CHD who received PGE1 in the Neonatal Intensive Care Department of Monastir between January 2014 and December 2023. Safety was assessed by the incidence, type, and severity of adverse events clinically attributed to PGE1.

Results: The hospital prevalence of duct-dependent CHD was 0.2%. The overall mortality rate was 51%, with 65% of deaths occurring preoperatively. Only 33% of cases had an antenatal diagnosis. PGE1 infusion was started at a mean age of 2.4 days. The mean initial and optimal maintenance doses were 0.067 mcg/kg/min and 0.028 mcg/kg/min, respectively. Adverse effects were frequent, with 85% of patients experiencing at least one event. The most common non-serious events were irritability (22%), fever (17%), and cutaneous flushing (16%). Serious adverse events included apnea (10%), hypotension (13%), and convulsions (5%).

Conclusion: PGE1 is an indispensable but high-risk therapy. Our findings highlight a substantial burden of adverse effects, even with low-dose regimens, and a critically high preoperative mortality. This underscores systemic challenges beyond drug safety alone. Improving outcomes necessitates a multifaceted strategy: enhanced antenatal screening, implementation of standardized PGE1 protocols to minimize risks, and optimized surgical pathways to reduce critical delays.

Keywords: Newborn / Congenital heart diseases / Ductus arteriosus / Prostaglandin E1 / Safety / Adverse effects / Intensive care

INTRODUCTION

Congenital heart diseases (CHD) are the most frequent birth defects, with a global prevalence of approximately 1% of live births. Among these, nearly a quarter are critical, representing a leading cause of infant mortality attributable to congenital anomalies [1-3]. A significant subset of critical CHDs is duct-dependent, where systemic or pulmonary blood flow relies on the patency of the ductus arteriosus (PDA). In these cases, clinical deterioration is often precipitous following postnatal ductal constriction [4]. Antenatal diagnosis, primarily via second-trimester echocardiography, is crucial for planning perinatal management and improving outcomes [5]. Duct-dependent lesions are anatomically categorized into three groups: those with duct-dependent pulmonary circulation (e.g., pulmonary atresia), systemic circulation (e.g., coarctation of the aorta, hypoplastic left heart syndrome), and mixing circulation (e.g., transposition of the great arteries) [6].

Prostaglandin E1 (PGE1) is the standard therapy to maintain ductal patency, serving as a vital bridge to palliative or corrective surgery. While life-saving, its use is complicated by a significant profile of adverse effects [6]. Data on the real-world safety profile and tolerance of PGE1, particularly in settings with varying resources and diagnostic delays, re-

Corresponding Author:
Dr Abdelmoula Siwar
faculty of medicine of Monastir

main valuable for optimizing clinical protocols. The primary objective of this study was to evaluate the safety and tolerance of prostaglandin E1 therapy in neonates with duct-dependent congenital heart disease in a real-life neonatal intensive care setting, with a focus on the incidence, type, and severity of adverse events. Clinical outcomes and mortality are reported as secondary, contextual findings.

METHODS

1) Study Design and Setting: A single-center, retrospective, descriptive, cross-sectional study was conducted in the Department of Intensive Care and Neonatal Medicine at the Monastir Teaching Hospital over a ten-year period (January 2014 – December 2023).

2) Population and Data Collection: The study included all newborns diagnosed with critical, duct-dependent CHD who received PGE1 to maintain ductal patency. Exclusion criteria encompassed incomplete medical records, stillborn babies, and outborn neonates who died prior to admission. Data was retrospectively collected from patient files using a pre-established, standardized data collection sheet. Data collection was performed by two investigators to ensure consistency, and discrepancies were resolved by consensus or by consulting a senior clinician.

3) Definitions and Variables:

- **Duct-dependent groups:** Patients were categorized into three pathophysiological groups based on circulatory dependency: Duct-dependent pulmonary circulation (Group 1), Duct-dependent systemic circulation (Group 2), and Duct-dependent mixing circulation (Group 3). A fourth group (Group 4) included neonates with suspected complex CHD who died before a formal cardiology diagnosis could be established.
- **Safety and Adverse Events:** The primary safety outcome was the occurrence of any adverse event clinically attributed to PGE1 infusion during the treatment period. Events were classified as **non-serious** (e.g., fever, flushing, irritability, edema) or **serious** (e.g., apnea requiring stimulation or intubation, hypotension requiring fluid bolus or vasopressors, convulsions). Imputability was based on temporal relationship to infusion start/stop or dose change, and exclusion of other obvious causes as documented in the medical record.
- **PGE1 Therapy:** The **optimal maintenance dose** was defined as the lowest dose documented to maintain adequate clinical and echocardiographic parameters of ductal patency and systemic perfusion for each individual patient.

4) Statistical Analysis:

Statistical analyses were performed using SPSS version 23.0. Qualitative variables were expressed as frequencies and percentages, and quantitative variables were summarized as means with standard deviations or medians with interquartile ranges, following normality assessment with the Kolmogorov-Smirnov test. Comparative analyses between groups were performed using Chi-square or Fisher's exact test for categorical variables, and ANOVA or Kruskal-Wallis test for continuous variables. A p-value <0.05 was considered statistically significant.

5) Ethical Considerations:

This retrospective analysis of anonymized clinical data was conducted in accordance with the principles of the Declaration of Helsinki. For this type of non-interventional study, formal approval from the ethics committee was not mandated by institutional regulations. Patient confidentiality was strictly maintained, and the requirement for informed consent was waived.

6) Ethical Considerations:

Conflict of interest: none.

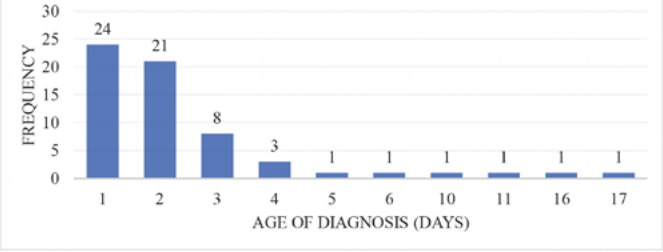
RESULTS

During the study period, 30 179 newborns were hospitalized in the intensive care and neonatal medicine department. Sixty-three newborns met the inclusion criteria, representing 0.2% of total hospitalizations. The cohort was classified into four groups: duct-dependent pulmonary circulation (Group 1, n=20), systemic circulation (Group 2, n=15), mixing circulation (Group 3, n=21), and undiagnosed complex CHD (Group 4, n=7).

1) Demographic characteristics:

The study cohort consisted of 63 newborns, with 23 infants (36.5%) being outborn referrals. A male predominance was observed (sex ratio 2:1). The mean gestational age was 38.3 weeks (range: 30-42 weeks). The mean birth weight was 3340g (range: 1200-4500g). Nearly two-thirds of the deliveries were by caesarean section. While 48 infants (76%) benefited from prenatal follow-up, only 21 (33%) received an antenatal diagnosis of critical CHD. The mean age at definitive diagnosis was 2.6 days (±3.15) (Figure 1).

Figure 1 : Age of patients at diagnosis



2) Clinical presentation and diagnosis:

In our cohort, common presenting signs did not differ significantly across study groups and included respiratory distress (76%), cyanosis (67%), and signs of poor perfusion (28%) (Table I).

si possible uniformiser la couleur utilisee pour les tableaux

Table 1 : Clinical presentation of 63 neonates with duct-dependent congenital heart disease, stratified by pathophysiology.

Clinical sign	Total Cohort (n=63)	Duct-Dependent Pulmonary Circulation (n=20)	Duct-Dependent Systemic Circulation (n=15)	Duct-Dependent Mixing Circulation (n=21)	Undiagnosed Complex CHD (n=7)
Cyanosis	42 (66.7%)	11 (55.0%)	7 (46.7%)	18 (85.7%)	6 (85.7%)
Respiratory distress	48 (76.2%)	13 (65.0%)	9 (60.0%)	19 (90.5%)	7 (100%)
Sign of poor perfusion	18 (28.6%)	7 (35.0%)	6 (40.0%)	3 (14.3%)	2 (28.6%)
Cardiac murmur	59 (93.7%)	20 (100%)	15 (100%)	16 (76.2%)	7 (100%)

A cardiac murmur was a near-ubiquitous finding, present in 94% of newborns. Echocardiography served as the definitive diagnostic modality. The distribution of specific heart defects is detailed in Table II.

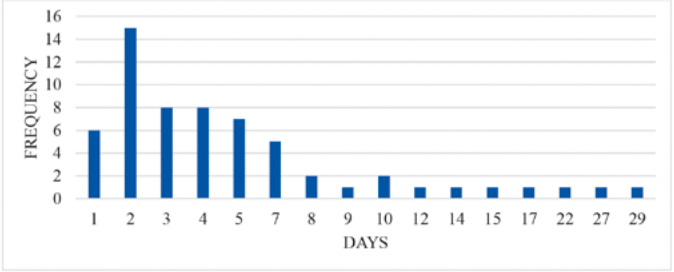
Table 2 : A cardiac murmur was a near-ubiquitous finding, present in 94% of newborns. Echocardiography served as the definitive diagnostic modality. The distribution of specific heart defects is detailed in Table II.

Physiopathologic Group	Specific Cardiac Defect	n	% of Group
Duct-Dependent Pulmonary Circulation (n=20)	○ Pulmonary atresia/stenosis	11	55.0%
	○ Tetralogy of Fallot with pulmonary atresia	8	40.0%
	○ Tricuspid atresia	1	5.0%
Duct-Dependent Systemic Circulation (n=15)	○ Coarctation of the Aorta (CoA)	10	66.7%
	○ Interruption of the Aortic Arc (IAA)	3	20.0%
	○ Hypoplastic left ventricle	1	6.7%
	○ Total anomalous pulmonary venous return	1	6.7%
Duct-Dependent Mixing Circulation (n=21)	○ Transposition of great artery (TGA)	20	95.2%
	○ Double outlet right ventricle	1	4.8%
Undiagnosed Complex CHD (n=7)	○ Complex cardiac anomaly (died before definitive diagnosis)	7	100%

3) Prostaglandin E1 therapy

PGE1 infusion was initiated at a mean age of 2.4 days (±2.65). The mean initial dose was 0.067 mcg/kg/min (±0.024). The mean optimal maintenance dose was 0.028 mcg/kg/min (±0.028). The mean treatment duration was 5.62 days (±5.88) (Figure 2).

Figure 2 : Duration of PGE1 use in newborns



A prolonged course of therapy exceeding 14 days was required for five patients (8%). Adverse effects were common, with 54 patients (85.7%) experiencing at least one event attributed to PGE1. Serious adverse events occurred in 17 patients (27%) and included apnea (10%, n=6), hypotension (13%, n=8), and convulsions (5%, n=3). Non-serious adverse events were frequent and included irritability (22%, n=14), fever (17%, n=11), cutaneous flushing (16%, n=10), gastrointestinal disturbances (10%, n=6), edema (8%, n=5), and hypocalcemia (6%, n=4). The mean time to onset of the first adverse effect was 5 hours. No statistically significant correlation was found between the initial PGE1 dose and the occurrence of apnea (p=0.42) or hypotension (p=0.38). Adverse event rates did not differ significantly between the three defined pathophysiological groups (p>0.05).

4) Clinical outcomes and mortality:

Surgical intervention was ultimately performed in 34 patients (54%). The procedures included a Blalock-Taussig shunt (17%, n=11), an arterial switch operation (20%, n=13) for transposition of the great arteries, and a Crafoord coarctation repair (11%, n=7). The overall mortality rate was high at 51% (n=32/63). Nearly two-thirds of these deaths (n=21/32, 65.6%)

Table 3 : Adverse events during PGE1 treatment, classified by severity.

Adverse Event	Total n (%)
Serious Adverse Event	**17 (27 %)**
- Apnea	6 (9.5 %)
- Hypotension	8 (12.7 %)
- Convulsions	3 (4.8 %)
Non serious Adverse Events	**54 (85.7 %)***
- Irritability/ Pain	14 (22.2 %)
- Fever	11 (17.5 %)
- Cutaneous flushing	10 (15.9 %)
- Gastrointastinal disturbances	6 (9.5 %)
- Edema	5 (7.9 %)
- Hypocalcemia	4 (6.3 %)

* Note: Patients often experienced more than one event; percentage refers to the proportion of the total cohort (N=63) experiencing at least one adverse event of any grade.*

occurred prior to any scheduled surgical intervention, highlighting the precarious preoperative period. The mean age at death was 6.69 days (±6.94), with a range from 1 to 29 days. The leading causes of death were septic shock (42%, n=13/32) and cardiogenic shock directly related to the underlying cardiac defect (38%, n=12/32). Notably, no death was primarily attributed to a direct complication of PGE1 therapy (e.g., refractory apnea or hypotension). However, PGE1-related side effects, particularly apnea and hypotension, were frequently documented as contributing comorbid factors in critically ill neonates who subsequently died from sepsis or cardiac failure. Mortality was further analyzed across the pathophysiological groups. It was highest in Group 4 (undiagnosed complex CHD, 86%, n=6/7) and Group 2 (duct-dependent systemic circulation, 67%, n=10/15), which includes conditions like hypoplastic left heart syndrome and critical coarctation. While this trend did not reach statistical significance (p=0.07) likely due to small sample sizes, it underscores the variable intrinsic risk associated with different cardiac anatomies.
The mean duration of hospitalization for the entire cohort was 13 days (±10.8 days), ranging from 1 to 49 days. For survivors who underwent surgery, the mean preoperative waiting time from admission/ PGE1 initiation to surgery was 7.2 days (±5.8).

DISCUSSION

This retrospective study provides a detailed evaluation of the safety and tolerance profile of PGE1 in a real-world cohort of 63 neonates with duct-dependent CHD. Our findings underscore a critical paradox: PGE1 is an indispensable life-sustaining therapy, yet its administration is associated with a formidable burden of adverse effects, occurring in 85% of patients. Furthermore, the context of care, characterized by frequent late diagnosis and significant preoperative mortality, highlights systemic challenges that extend beyond pharmacologic safety alone. The clinical trajectory of these infants was often precarious. The low rate of antenatal diagnosis (33%) and the mean postnatal age at diagnosis of 2.6 days reflect a persistent gap in early detection, consistent with challenges reported in other settings [4-7]. This delay directly affects the timing of PGE1 initiation and establishes a high-risk preoperative period. In our cohort, the overall mortality was 51%, with nearly two-thirds of deaths occurring before scheduled surgery. This alarming preoperative mortality rate underscores the vulnerability of neonates during the "bridge" to surgery and emphasizes that the success of PGE1 therapy is contingent on a timely and efficient surgical pathway [8-10]. Our data contribute to the ongoing refinement of PGE1 dosing strategies. The mean initial dose of 0.067 mcg/kg/min and, more notably, the mean optimal maintenance dose of 0.028 mcg/kg/min are lower than historical recommendations [11, 12]. This aligns with contemporary evidence supporting the efficacy of lower-dose regimens (0.005–0.09 mcg/kg/min) to maintain ductal patency while potentially mitigating toxicity [13-17]. Our observed spectrum of frequent Our data contribute to the ongoing refinement of PGE1 dosing strategies. The mean initial dose of 0.067 mcg/kg/min and, more notably, the mean optimal maintenance dose of 0.028 mcg/kg/min are lower than historical recommendations [11, 12]. This aligns with contemporary evidence supporting the efficacy of lower-dose regimens (0.005–0.09 mcg/kg/min) to maintain ductal patency while potentially mitigating toxicity [13-17]. Our observed spectrum of frequent adverse effects, led by irritability (22%), fever (17%), and flushing (16%), aligns with established

reports [18, 19]. However, the incidence of serious events, including apnea (10%) and hypotension (13%), remains a significant concern. Contrary to some studies [16, 18, 20], we did not find a statistically significant correlation between the initial PGE1 dose and the occurrence of apnea or hypotension, suggesting that individual patient susceptibility and other clinical factors may be as influential as dose alone. This finding reinforces the principle of titrating to the lowest effective dose for each patient. The high mortality observed was multifactorial. No death was primarily attributed to a direct complication of PGE1. Instead, mortality was driven by the underlying cardiac disease (cardiogenic shock, 38%) and associated critical illnesses, most notably septic shock (42%). This pattern indicates that while PGE1-related side effects are a major management challenge, the ultimate outcome for these neonates is heavily influenced by the severity of the cardiac defect, the risk of nosocomial complications during prolonged hospitalization, and crucially, the time to definitive surgical intervention. Our experience mirrors the complex interplay of factors described in similar resource-constrained settings [21].

Limitations of the Study

This study has several limitations inherent to its retrospective, single-center design over a decade. The sample size, while substantial for our center, limits the power for subgroup analyses. Evolving clinical and surgical practices during the study period may affect the homogeneity of management. Furthermore, the attribution of adverse effects, though based on clinical documentation, can be challenging to ascertain retrospectively. Despite these limitations, our study offers valuable real-life insights into the challenges of managing duct-dependent CHD.

CONCLUSION

This study confirms that PGE1 therapy, while life-saving, carries a substantial burden of adverse effects, even with optimized low-dose regimens. The high mortality observed is multifactorial, strongly linked to late diagnosis and preoperative delays rather than to drug safety alone. To improve the global care pathway for these neonates, a multifaceted approach is essential: (1) enhancing antenatal screening programs to enable planned perinatal management, (2) implementing and adhering to standardized PGE1 protocols focused on using the minimum effective dose to mitigate risks, and (3) strengthening collaborative networks between neonatal and cardiac surgical teams to minimize critical waiting times. Prospective studies are needed to validate protocols that optimize the safety bridge to surgery.

List of abbreviations

CHD: congenital heart disease
CoA: coarctation of the aorta
IAA: interrupted aortic arch
PDA: patency of ductus arteriosus
PGE1: prostaglandin E1
TGA: transposition of great arteries

REFERENCES :

[1] Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39(12):1890–900.

[2] Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. Pediatrics. 2013;131(5):e1502-1508.

[3] Taksande A, Jameel PZ. Critical Congenital Heart Disease in Neonates: A Review Article. Curr Pediatr Rev. 2021;17(2):120–6.

[4] Yun SW. Congenital heart disease in the newborn requiring early intervention. Korean J Pediatr. 2011;54(5):183–91.

[5] American Institute of Ultrasound in Medicine. AIUM practice guideline for the performance of obstetric ultrasound examinations. J Ultrasound Med. 2010;29(1):157–66.

[6] Akkinapally S, Hundalani SG, Kulkarni M, Fernandes CJ, Cabrera AG, Shivanna B, et al. Prostaglandin E1 for maintaining ductal patency in neonates with ductal-dependent cardiac lesions. Cochrane Database Syst Rev. 2018;2018(2):CD011417.

[7] Chang RK, Gurvitz M, Rodriguez S. Missed diagnosis of critical congenital heart disease. Arch Pediatr Adolesc Med. 2008;162(10):969–74.

[8] Singh Y, Mikrou P. Use of prostaglandins in duct-dependent congenital heart conditions. Arch Dis Child Educ Pract Ed. 2018;103(3):137–40.

[9] Yee L. Cardiac Emergencies in the First Year of Life. Emergency Medicine Clinics of North America. 2007;25(4):981–1008.

[10] Knowles R, Griebsch I, Dezateux C, Brown J, Bull C, Wren C. Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2005;9(44):1–152.

[11] Roehl SL, Townsend RJ. Alprostadil (Prostin VR Pediatric Sterile Solution, The Upjohn Company). Drug Intell Clin Pharm. 1982;16(11):823–32.

[12] Heymann MA, Rudolph AM. Ductus arteriosus dilatation by prostaglandin E1 in infants with pulmonary atresia. Pediatrics. 1977;59(3):325–9.

[13] Yucel IK, Cevik A, Bulut MO, Dedeoğlu R, Demir İH, Erdem A, et al. Efficacy of very low-dose prostaglandin E1 in duct-dependent congenital heart disease. Cardiol Young. 2015;25(1):56–62.

[14] Huang FK, Lin CC, Huang TC, Weng KP, Liu PY, Chen YY, et al. Reappraisal of the prostaglandin E1 dose for early newborns with patent ductus arteriosus-dependent pulmonary circulation. Pediatr Neonatol. 2013;54(2):102–6.

[15] Silove ED, Roberts DG, de Giovanni JV. Evaluation of oral and low dose intravenous prostaglandin E2 in management of ductus dependent congenital heart disease. Arch Dis Child. 1985;60(11):1025–30.

[16] Singh GK, Fong LV, Salmon AP, Keeton BR. Study of low dosage prostaglandin--usages and complications. Eur Heart J. 1994;15(3):377–81.

[17] Haughey BS, Elliott MR, Wiggin JY, Conaway MR, White SC, Swanson JR, et al. Standardizing Prostaglandin Initiation in Prenatally Diagnosed Ductal-Dependent Neonates; A Quality Initiative. Pediatr Cardiol. 2023;44(6):1327–32.

[18] Badheka A, Bangalore Prakash P, Allareddy V. Prostaglandin E1-Induced Periostitis and Reversibility with Discontinuation. J Pediatr. 2017;189:237-237.e1.

[19] Kramer HH, Sommer M, Rammos S, Krogmann O. Evaluation of low dose prostaglandin E1 treatment for ductus dependent congenital heart disease. Eur J Pediatr. 1995;154(9):700–7.

[20] Gordon CM, Tan JT, Carr RR. Effectiveness of Alprostadil for Ductal Patency. J Pediatr Pharmacol Ther. 2024;29(1):37–44.

[21] Cucerea M, Simon M, Moldovan E, Ungureanu M, Marian R, Suciu L. Congenital Heart Disease Requiring Maintenance of Ductus Arteriosus in Critically Ill Newborns Admitted at a Tertiary Neonatal Intensive Care Unit. J Crit Care Med (Targu Mures). 2016;2(4):185–91.