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Review Article

Paediatrics Section

Use of Prostaglandin E1 in Neonates with Severe Persistent Pulmonary Hypertension (PPHN): A Narrative Review

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ABSTRACT

Persistent Pulmonary Hypertension of the Newborn (PPHN) is a significant health issue characterised by the inadequate circulatory transitions at birth, subsequent to considerable hypoxaemia and increased Pulmonary Vascular Resistance (PVR). Inhaled Nitric Oxide (iNO) is the preliminary treatment approach; however, it fails to achieve favourable outcomes in approximately 30-40% of neonates. Consequently, therapeutic alternatives, particularly Prostaglandin E1 (PGE1), are capturing attention for their considerable vasodilatory features and capability to maintain Ductus Arteriosus (DA) patency. Additionally, PGE1 decreases right ventricular afterload and augments systemic oxygen delivery, thus functioning as a valuable option for managing PPHN in this vulnerable population. This review article aims to comprehensively determine the intricate role of PGE1 in the context of PPHN, focusing on its pathophysiology, clinical utility and novel treatment methods. The study also examines current research concentrating on optimising PGE1 protocols, including dosage clinical guidelines and evaluating potential long-term complications, with the objective of enhancing paediatric care through both established practices and innovative strategies.

Keywords: Neonates, Prostaglandin E1, Pulmonary hypertension, Vascular resistance, Vasodilatory

INTRODUCTION

The PPHN is a debilitating condition characterised by acute respiratory distress and significantly decreased blood oxygen levels post-birth. It causes increased pulmonary artery pressure in the absence of cyanotic congenital cardiac defects and is correlated with right-to-left blood flow through fetal circulatory mechanisms, involving the DA and foramen ovale, after pulmonary vasoconstriction [1]. The prevalence of PPHN is 1.8 per 1000 live births, with 5.4 per 1000 live births of late preterm infants, in comparison to term infants at 1.6 per 1000 live births, with reported mortality ranges between 7.6% to 10.7% [2].

The annual prevalence of PPHN in India ranges from 0.4 to 6.8 per 1000 live births, with mortality rates ranging between 4% and 33% [3]. PPHN is associated with numerous risk factors, including maternal diabetes and obesity, perinatal complications like meconium aspiration syndrome, and neonatal infections [4]. PPHN develops from a malformed decrement in PVR after birth, resulting in insufficient oxygenation [5]. The standard management for PPHN includes reducing pulmonary pressure and oxygenation, using oxygen therapy, iNO, and Extracorporeal Membrane Oxygenation (ECMO). Nearly 30%-40% of neonates represent indifference with administering pharmacological agents, including Nitric Oxide (NO), and sildenafill, and ECMO therapy, which is associated with hypotension, bleeding, and inadequate neurocognitive outcomes. Standard therapies notably augment morbidity and mortality rates, while also increasing substantial costs [5].

PGE1 is vital in managing PPHN by facilitating right-to-left shunting, maintaining ductal patency, and reducing right ventricular afterload. Recent literature suggests that PGE1 effectively stabilises neonates with severe PPHN, particularly cases limited by conventional treatments, without any significant Adverse Events (AEs) [6]. This review aims to comprehensively demonstrate the role of PGE1 in treating severe PPHN, including addressing the pathophysiology of PPHN, its clinical applications, mechanisms of action, safety, and efficacy in relation to different vasodilators. In addition, the study focused on emergent therapeutic modalities and potential progression in managing PPHN to enhance neonatal outcomes.

PATHOPHYSIOLOGY OF PPHN

The PPHN is an intricate process leading to elevated PVR and decreased Pulmonary Blood Flow (PBF) with compromised oxygenation. This may lead to hypoxia, acidosis, cyanosis, and reduced end-organ perfusion. Hypoxaemia and acidosis increase PVR, developing a self-reinforcing cycle. Increased PVR continuously elevates the workload on the Right Ventricle (RV), causing hypertrophy and, if prolonged, leading to RV dilation and failure, worsening PBF reduction and hypoxaemia [7].

Increased PVR may arise from abnormal pulmonary vasoconstriction, structural remodelling of the pulmonary vasculature, lung hypoplasia, or intravascular obstruction, such as polycythemia. In moderate to severe PPHN, PVR frequently surpasses systemic vascular resistance, enabling right-to-left shunting of deoxygenated blood through DA and foramen ovale, resulting in significant hypoxaemia. The bi-directional nature of the foramen ovale shunt leads to evaluating total anomalous voluminous return in cases of right-to-left shunting [7].

Endothelial dysfunction is an important factor, as the endothelium develops vasodilators, including NO and prostacyclin, sustaining reduced PVR. In PPHN, reduced vasodilator production and increased levels of vasoconstrictors, such as endothelin-1, could cause persistent vasoconstriction and vascular remodelling, featured by elementary thickening, medial hypertrophy, and fibrosis [8].

CURRENT TREATMENT STRATEGIES

Management techniques for PPHN have significantly progressed, focusing on enhancing PBF and mitigating hypoxic injury [5]. Sildenafil, a phosphodiesterase-5 inhibitor (PDE5), functions as an alternative to iNO and enhances NO signalling and PDE-5 activity, beneficial for patients experiencing prolonged hyperoxic breathing [9]. In infants with co-existent DA-dependent circulation, PGE1 administration maintains ductal patency and decreases RV afterload. Additionally, PGE1 is correlated with reduced levels of Brain Natriuretic Peptide (BNP) over time and elevated echocardiographic parameters of RV and pulmonary hypertension function [6]. Other pharmaceutical substitutes comprise milrinone,

a PDE-3 inhibitor, and bosentan, an endothelin receptor antagonist, which assists in elevating myocardial contractility and decreasing PVR [6]. Nevertheless, current evidence, primarily derived from case studies and clinical trials, is limited among neonates [1,6]. Supportive therapeutic alternatives, including oxygen therapy, high-frequency ventilation, surfactant therapy, and ECMO, direct rescue interventions for neonates experiencing severe and refractory PPHN [8].

Role of Prostaglandin E1 (PGE1) in Neonatal Care

PGE1 intervention is significant in neonatal care and is commonly employed in infants with ductal-dependent Congenital Heart Disorders (CHD) to maintain ductal patency, thereby facilitating appropriate pulmonary or systemic blood flow [10]. PGE1 has shown significance in neonates with conditions including congenital diaphragmatic hernia and PPHN without significant AEs [6]. In these neonates, PGE1 functions as a process to decrease supra-systemic RV pressures and increase cardiac performance. The capacity of PGE1 to generate induced pulmonary vasodilation via elevated cyclic Adenosine Monophosphate (cAMP) synthesis, improving its therapeutic importance [10]. Despite these benefits, administering PGE1 requires thorough evaluation due to potential AEs including hypotension, apnea, and fever, specifically at increased dosages [6].

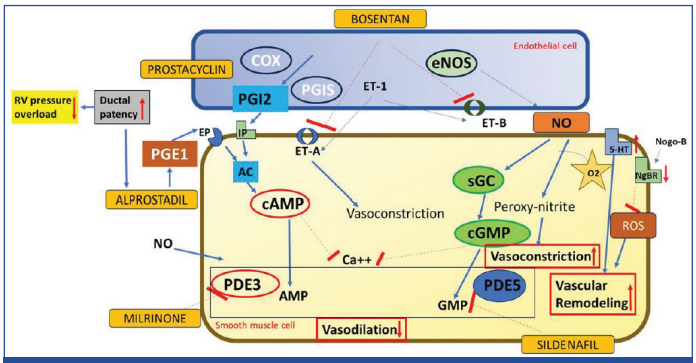
MECHANISM OF ACTION

Arachidonic Acid Prostacyclin cAMP pathway: The arachidonic acid-prostacyclin-cAMP pathway modulates vascular and pulmonary tone. Prostaglandins increase intracellular cAMP levels in Pulmonary Artery Smooth Muscle Cells (PASMCs) by activating adenylyl cyclase, causing vasodilation, necessary for fetal circulation and contributing to PVR reduction post-birth [11]. Cyclooxygenases (COX-1 and COX-2) metabolise arachidonic acid for generating prostanoids, including Prostacyclins (PGI2) and PGE2, involved in regulating vascular tone [12]. Disrupting the arachidonic acid-prostacyclin pathway in PPHN obstructs vasodilation and leads to increased PVR. PGI2 serves as a potential vasodilator by activating adenylyl cyclase, thereby improving cAMP distribution, ultimately inducing vascular smooth muscle relaxation. PPHN neonates exhibit decreased PGI2 receptor expression and pulmonary prostacyclin synthase, causing reduced responsiveness to PGI2 analogues. Restoring system via utilising prostacyclin analogues or PDE-3 inhibitors, such as milrinone, has been proposed as a potent treatment strategy in elevating cAMP levels, thereby improving pulmonary vasodilation [11].

Vasodilatory Effects

PGE1 is a bioactive molecule featured by its vasodilatory, antiproliferative, antiplatelet, and anti-inflammatory properties. PGI2 is advantageous for both pre-term and term newborns, in addition to children experiencing increased pulmonary pressures [13]. PGE1 serves as a pulmonary vasodilator, targeting dysregulated pulmonary regions, thereby enhancing efficacy and decreasing AEs [14]. Moreover, PGE1 increases oxygenation with decreased PVR, dilating both systemic and pulmonary arteries via numerous processes. This bidirectional pathway encompasses rapid vasodilation and sustained impacts mediated by agents including endothelin, NO, and angiotensin II [14] [Table/Fig-1]. PGE1 enhances cAMP levels in PASMCs via activating EP2 and EP4 receptors, and smooth muscle cell relaxation [11,12]. Additionally, it elevates RV functionality and decreases Pulmonary Arterial Hypertension (PAH) associated remodelling [6,14].

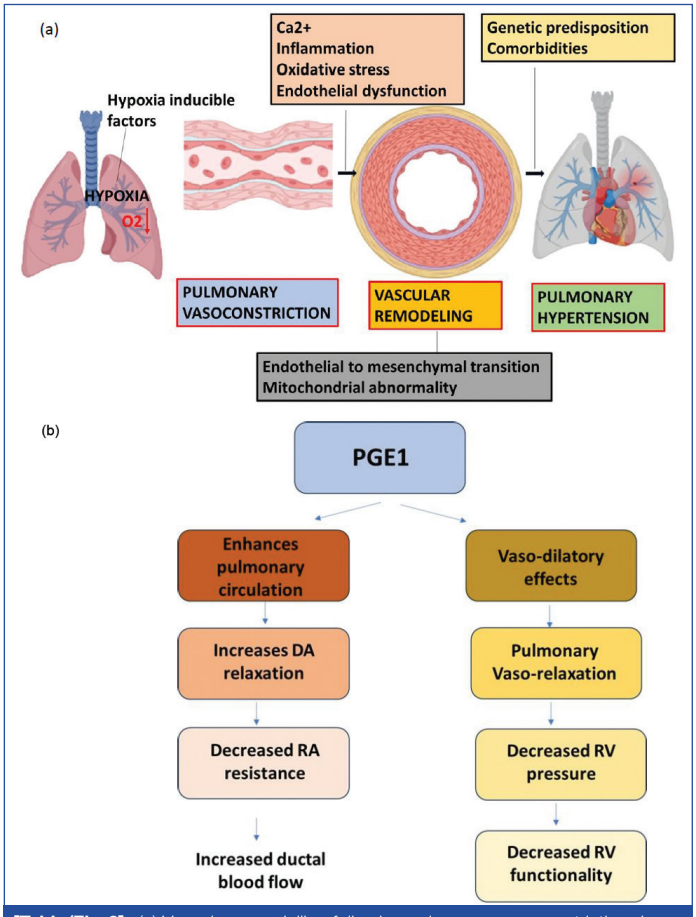
Abbreviation: AC: Adenylylcyclase; AMP: Adenosinemonophosphate; cAMP: cyclic Adenosine monophosphate; cGMP: cyclic Guanosine monophosphate; COX: Cyclooxygenase; EP: NO: nitric oxide; PGE1-receptor; IP: PGI2-receptor; PDE3: Phosphodiesterase-3; PDE5: Phosphodiesterase-5; PGE1, prostaglandin E1; PGES: PGE1 synthase; PGI2: prostacyclin; PGIS: PGI2 synthase; ROS: reactive oxygen species; RV: right ventricle (Source: modified from Martinho S et al., [11], and Sharma V et al., [15].



[Table/Fig-1]: Pathogenic mechanisms of PPHN representing effects of different potent vasodilators.

Effects on Pulmonary Circulation

The PGE1 improves pulmonary circulation by two-fold mechanisms, initially by inducing DA relaxation, which reduces DA resistance, resulting in increased blood flow across DA; secondly, through non-specific vasodilatory effects, such as pulmonary vaso-relaxation, reducing PVR and pressure, causing reduced right-to-left blood flow rates through DA [Table/Fig-2] [16-18]. PGE1 may increase left ventricular function by enhancing diastolic filling and PBF, and decreasing RV pressure, thereby elevating left ventricular preload. With DA re-opening and subsequent decrement in pressure within the pulmonary arteries, and reduced PVR causes improved PBF. An increased left ventricular output improves mixed venous oxygen saturation and oxygen delivery, which aids in sustaining pulmonary vasodilation and preventing post-ductal desaturation during right-to-left shunting through DA [15-20].



[Table/Fig-2]: (a) Vascular remodelling following pulmonary vasoconstriction during hypoxia in PPHN; and (b) Effects of PGE1 on pulmonary circulation [18].
DA: Ductus arteriosus; PGE1: Prostaglandin-E1; RV: Right ventricle.
Source: modified from Nakamura K et al.

Comparison with Other Vasodilators

Therapeutically managing PPHN is dependent on primary clinical objectives, including reduced PVR, which enhances oxygenation, PBF, and cardiac outcomes, leading to haemodynamic stability. Moreover, eliminating PPHN-related outcomes, including RV failure and end-organ destruction, leads to favourable long-term results. These therapeutic goals facilitate the employment and selection of multiple pharmacological therapies in clinical settings [6]. An overview of other vasodilators is provided in [Table/Fig-3] [5,8,11,21-28].

Drug Therapy	Advantages	Limitations	Mechanism
Sildenafil	Effective through oral and enteral administration, and used as an adjunct to iNO	Limited neonatal data and systemic hypotension	Stimulates cyclic Guanosine Monophosphate (cGMP) production in pulmonary vascular smooth muscle cells by blocking PDE5 and improving endogenous NO activity. Additionally, lowers the remodelling of the pulmonary vascular system by inhibiting the growth of vascular smooth muscle cells [5,8].
Inhaled Nitric Oxide (iNO)	Systemic pulmonary vasodilation	Does not enhance survival, and approximately 40% of infants remain non-responsive to treatment.	Activates soluble Guanylyl Cyclase (sGC) in smooth vascular muscle, resulting in a rise in cGMP. It then activates protein kinase G, which stimulates myosin phosphatase, opens K^+ channels (hyperpolarisation), and reduces Ca^{2+} influx, resulting in vasodilation [8,11].
Bosentan	An effective and safe therapy for increasing oxygen saturation (SpO_2) and Oxygenation Index (OI) in neonates with PPHN. Used with iNO as an adjuvant treatment	Pulmonary haemorrhage, liver dysfunction, or systemic hypotension.	A dual endothelin receptor antagonist that prevents vasoconstriction and indirectly promotes pulmonary vasodilation [21-23].
Milrinone	As an adjunct to iNO therapy, or as a monotherapy.	Systemic hypotension and limited pharmacokinetic data of Milrinone in infants.	A PDE3 inhibitor and bipyridine analogue of amrinone functions as a lusitrope that enhances diastolic function and causes vasodilation in the systemic and pulmonary artery beds [24].
Prostaglandin analogues (e.g., Treprostinil, Beraprost sodium)	Used to treat pulmonary arterial hypertension in adults and has a potential antiplatelet effect.	Limited data on the acute therapy of PPHN using treprostinil, while there is no data for premature newborns.	A stable homologue of prostacyclin (Treprostinil) causes vasodilation of systemic and pulmonary vascular beds and thereby decreases platelet aggregation [25,26]. Prostacyclin oral derivative (Beraprost sodium) tends to lower pulmonary arterial pressure and PVR in the management of secondary pulmonary hypertension, particularly in Congenital Heart Disorders (CHD) [27].
sGC stimulators/ activators	Used as monotherapy or in conjunction with prostanoids to treat pulmonary arterial hypertension.	Headache, peripheral oedema, nasopharyngitis, and hypotension.	Improves vasodilation and lowers pulmonary arterial pressure by upregulating the sGC-NO cGMP pathway [5,8].
Rho-Kinase inhibitors	Prevents pulmonary vascular remodelling, and pulmonary vasodilation and improves endothelial function.	Requires further investigation into potential AEs and long-term safety concerns in neonatal PPHN	Impacts endothelial function and angiogenesis by modifying Rho kinase activity [8,28].

[Table/Fig-3]: An overview of pharmacological vasodilators for the treatment of PPHN [5,8,11,21-28].

Non-Pharmaceutical Intervention

Non-pharmaceutical therapeutic strategies are vital in comprehending PPHN as they assist in improving oxygenation and reducing PVR. Oxygen therapy involves mechanical and high-frequency ventilation and helps in regulating desirable oxygenation while decreasing pulmonary injuries. Surfactant treatment assists neonates in evading respiratory distress syndrome by elevating pulmonary compliance. Another strategy, namely, ECMO, is a life-saving intervention for severe PPHN incidents, fail to respond to standard therapy. Moreover, supportive therapy, involving fluid management and sedation techniques, facilitates haemodynamic stability and reduces metabolic requirement [5].

CLINICAL APPLICATIONS OF PGE1 IN NEONATES WITH SEVERE PPHN

Indications for Use

PGE1 is specifically beneficial in incidents of pulmonary vasoconstriction, including Congenital Diaphragmatic Hernia (CDH), meconium aspiration syndrome, and neonatal sepsis [6]. In neonates with Duct-Dependent Congenital Heart Disease (DDCHD), PGE1 is administered prophylactically to facilitate systemic and pulmonary circulations [29]. Also, it is advantageous in instances when conventional treatments, including iNO, failed to reduce PVR or improve oxygenation [6].

Dosage and Administration

PGE1 is administered intravenously as a continuous infusion, with evidence suggesting a dose between 50 and 100 ng/kg/minute. Treatment with a reduced dose of PGE1 (20 ng/kg/minute) initially and a maintenance dose of 10 ng/kg/minute is recommended for early neonates experiencing CHD and DA-dependent pulmonary circulation [30]. Echocardiography is utilised to regulate ductal patency, RV functionality by Fractional Area Change (FAC), and RV afterload by Pulmonary Artery Acceleration duration indexed to Right Ventricular Ejection Time (PAAT/RVET) ratio [6]. The extent of the infusion variability is dependent upon the severity of the condition, with most neonates demanding 24 to 72 hours of treatment prior to PVR stabilisation [6]. AEs, including hypotension, convulsion, apnoea or cortical hyperostosis, are directed by decreasing the dosage requirement and modifying the infusion regions [31].

REVIEW OF CLINICAL STUDIES AND EVIDENCE-BASED OUTCOMES

The therapeutic efficacy of PGE1 in PPHN cases has been widely examined. For instance, Sood BG et al., assessed the feasibility, safety, and efficacy of PGE1 among newborns with hypoxaemic respiratory failure attributed to PPHN. Infants with an oxygenation index between 15 and 25, who had not been administered iNO, were randomised to receive either PGE1 or a placebo. However, the trial was terminated early due to limited recruitment and most of them relied on iNO treatment [13]. An updated protocol recommended

PGE1 co-administration with iNO for a duration of up to 72 hours at dosages of 150 or 300 ng/kg/min involving seven infants with minor protocol deviations and no significant AEs recorded [32].

A retrospective analysis by Gupta N et al., revealed that newborns aged 10 days or younger with PPHN and/or DDCHD were administered with PGE1. The fraction of inspired oxygen levels reduced significantly during transit; however, no other physiological factors were noted, highlighting PGE1's significance in preserving haemodynamic stability during newborn transport [33].

Another retrospective cohort analysis by Tsoi SM et al., examined PGE1 efficacy in 57 infants with PPHN and revealed a significant improvement in echocardiographic measures, particularly PAAT/RVET. Additionally, a significant improvement in oxygen saturation and end-organ perfusion within 24 hours of treatment commencement suggested a direct role of PGE1 in haemodynamic stabilisation. However, no AEs were reported, supporting its use as an effective adjunct in severely managing PPHN [6].

Huang FK et al., investigated the safety and efficacy of low-dose PGE1 therapy in 33 newborns diagnosed with CHD and PDA-dependent pulmonary circulation. An initial dose of 20 ng/kg/min preserved ductal patency significantly while minimising AEs. In the low-dose group (10.5±5.3 ng/kg/min), notable improvements were recorded in the partial pressure of oxygen (26.48-40.85 mmHg) and SpO_2 levels (69%-85%), with mild AEs, including fever, seizures, hypotension, or apnoea, reported. In contrast, in infants administered with higher doses (39±13.2 ng/kg/min), three out of eight needed intubations due to apnoea [30].

In a case series, Lewis AB et al., reported that 75% of newborns experiencing CHD revealed a positive response to PGE1 administration, resulting in significantly increased levels of PO_2 (136%), specifically in RV outflow obstruction cases. Moreover, neonates exhibiting compromised vascular circulation revealed improvements in arterial blood pressure, urine output, and peripheral perfusion, indicating effective stabilisation of PGE1. AEs, including vasodilation, pyrexia, and myoclonic jerks, were reported and monitored according to infusion rate and administration site [34].

SAFETY PROFILE AND POTENTIAL ADVERSE EFFECTS

Common AEs

Multiple studies have investigated the safety profile of PGE1 in PPHN cases, and evidence reveals that PGE1 is generally well-established. The short-term AEs include hyperthermia and bleeding occurring during the therapy commencement. Other possible neurological AEs include agitation, seizures, and apnoea. Gastrointestinal hitches include diarrhoea, necrotising enterocolitis, and gastric antral mucosal hypertrophy. Cardiovascular effects, including flushing, heart failure, cutaneous vasodilation, tachycardia, bradycardia, hypotension, and arrhythmia, are also vital. The long-term AEs of PGE1 over five days have been associated with mucosal injury, brown fat necrosis, abdominal outlet blockage, and cerebral hyperostosis. Moreover, the right-to-left ductal shunting may lead to elevated hypoxia. Histological evaluations from autopsy or surgery have established evidence of vascular damage, including medial oedema, haemorrhage, preliminary tears, and destruction of the internal elastic lamina [10,35,36].

Risks and Contraindications

Evidence recommends the hazards and contraindications linked with PGE1 therapy. Stone DM et al., observed a concession of renal perfusion by PGE1, causing pre-renal failure and pulmonary edema. Flushing and temporary erythematous rash were primary AEs requiring close regulation [37]. Cole R et al., noticed an elevated threat of DA variability and division with consistent PGE1 administration, potentially leading to surgical barriers or spontaneous aneurysms, specifically severe PPHN cases [38]. Heymann MA and Clyman RI explained systemic effects of PGE1, such as apnea, hypotension, neurocognitive events, and peripheral vasodilation. They emphasised that neonates <2.0 kg birth-weight or with bleeding predispositions are at higher vulnerability to AEs [39]. Goddard-Finegold J et al., revealed that PGE1 may lead to microvascular injury and pulmonary arteritis due to infections. In severe PPHN, the hazards may offset advantages, demanding a comprehensive risk-benefit evaluation before utilisation [40]. Alhussin W and Verklan MT reported that 91% of neonates experienced AEs, including hypotension, apnoea, hypokalaemia, bradycardia, and heart failure. Moreover, cortical hyperostosis and gastric outlet obstruction observed in severe cases necessitate timely intervention and vigilant monitoring during prolonged PGE1 therapy [41].

Strategies for Minimising Adverse Events (AE)

The PPHN management requires effective strategies to reduce AEs. Kaplish D et al., highlighted that appropriate dosing and vigilant AEs monitoring are essential. PGE1 dose titration assists in evaluating therapeutic response while minimising complications. Combining PGE1 with other therapies, including iNO, may improve efficacy and permit lower dosages, thus decreasing AEs [5]. Tsoi SM et al., emphasised that monitoring haemodynamics during PGE1 use, specifically for indications like tachycardia and lactic acidosis, may improve post-initiation outcomes and reduce AEs [6]. Shlomai ON et al., noted that lower doses of PGE1 (0.01-0.03 mcg/kg/min) maintain ductal patency with lesser AEs [36]. Similarly, Vari D et al., revealed that dosage initiation at 0.01 µg/kg/minute was safe and effective, although respiratory depression was more significant among preterm infants, demanding cautious monitoring and personalised dose modifications [42]. Additionally, Mandell E et al., suggested that iNO utilisation alongside PGE1 could decrease higher dose requirements and associated AEs [43].

FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

Emerging Therapies and Combination Approaches

Emerging therapeutic strategies improve outcomes in severe PPHN cases. Riociguat, a sGC stimulator, improves the NO signalling pathway and facilitates vasodilation among NO-resistant patients. In addition, sGC activators, including cinaciguat, offer an NO-independent method for promoting vasodilation, particularly under oxidative stress conditions with limited NO production [11,44]. Rho-kinase inhibitors, including fasudil, decrease PVR by targeting smooth muscle hyper-contractility. Despite their benefits among adults, trials on newborns with PPHN are limited. In addition, L-citrulline supplementation, enhancing endogenous NO synthesis by recycling L-arginine, has been depicted as promising in pre-clinical models by improving efficiency and reducing PVR among PAH cases [11]. Endothelin receptor antagonists, including ambrisentan and bosentan, activate endothelin receptors in smooth muscle cells, causing elevated ionic concentration of calcium and vasoconstriction, as well as treating PAH in infants and toddlers [8,44]. In comparison to monotherapies, utilising PGI2 in iNO-resistant newborns has revealed positive outcomes, without the need for ECMO [11].

Prostacyclins, including treprostinil and epoprostenol, show considerable anti-inflammatory and vasodilatory effects via the cAMP pathway. Iloprost and other inhaled prostacyclin analogs deliver pulmonary discernment after systemic hypotension. Recent literature supports utilising prostacyclin analogs in combination with PDE inhibitors for achieving synergistic vasodilatory effects. Sildenafil in combination with milrinone or bosentan has depicted enhanced oxygenation and survival in refractory PPHN incidents, although hypotension poses a significant risk [5,44]. Moreover, this combination provides haemodynamic stability and lung recovery

in severe cases requiring ECMO [5]. Such novel medications and combination techniques establish an extensive progression in PPHN management, developing new strategies for neonates impassive to conventional methods.

Genetic and Biomarker Research

Recent genetic and biomarker evidence offered beneficial insights into the underlying mechanisms of PPHN cases. Nakwan N et al., in a genome-wide association study, demonstrated the WW and C2 domain-containing protein 2 (WWC2) gene as an important region, with the Single Nucleotide Polymorphism (SNP) rs149768622 (T>C) associated with PPHN. WWC2 is associated with alveolar development and pulmonary remodeling, indicating its role in PPHN pathophysiology [45]. Additional SNPs correlating with PPHN include variations in Carbamoyl Phosphate Synthase-I (CPS-I) (rs192759073, rs1047883, rs2229589) and NOTCH3 (rs1044008), influencing NO production and cellular proliferation, important for controlling PVR. Rare variations in TBX4, BMPR2, SMAD9, and KCNA5 further accentuate the roles of ion-channel regulation and Bone Morphogenetic Protein/Transforming Growth Factor Beta (BMP/TGF-β) signalling pathways in PPHN progression [46].

Genetically screening variations in genes, including WWC2 and endothelin 1, could ensure rapid determination and control of susceptible neonates. Pre-term infants with PPHN often display exclusive genetic profiles overlapping with bronchopulmonary dysplasia and respiratory distress syndromes, highlighting the significance of targeted therapeutic strategies [46]. Jano E et al., discovered potential biomarkers, including miRNA-126a-5p, BNP, troponin, and galectin-3, suggesting that increased BNP and troponin levels were significantly linked with PPHN, highlighting their importance in rapid early diagnosis [47]. Similarly, El-Khazragy N et al., depicted a strong correlation between CPS-I gene polymorphism (A/C, rs4399666) and idiopathic PPHN among Egyptian neonates, with the CC genotype associated with decreased iNO levels, commonly seen in PPHN cases. This highlights the role of CPS-I gene variants in disease susceptibility and serves as a potential biomarker for risk stratification among affected newborns [48].

Innovations in Drug Delivery

Recent progress in drug delivery systems improves the efficacy and safety of PGE1 therapy, concentrating on aerosolised formulations, nanoparticle-based strategies, and sustained-release methods. Aerosolised PGE1 formulations permit targeted delivery to the lungs, facilitating selective vasodilation while reducing AEs [13]. Preliminary trials have suggested enhancements in oxygenation, with a notable increase in arterial oxygen tension among neonates with infused PGE1 prior to iNO [32,44]. However, safeguarding and consistency are vital, as ceasing aerosolised PGE1 could have negative effects. Nebulisers and delivery systems are important for reducing the risk of recurrent PPHN [13]. Nanotechnology has facilitated generating polymeric particles and liposomal formulations, reinforcing PGE1 stability, and improving targeted delivery with reduced AEs. Liposomal-based formulations utilising hydrophilic polymers and cyclodextrin assist in increasing PGE1 transport and efficacy. Moreover, micelle-based formulations utilising polyglycol-derived phospholipids facilitate continuous drug release with improved entrapment efficiency [49]. Targeted delivery systems utilising PGE1-derived nanoparticles further reduce systemic exposure, enhancing treatment outcomes [50].

Potential Role in Preterm Neonates with PPHN

The PGE1 plays an important role in treating preterm neonates with PPHN. PGE1 administration maintains RV function while evading further haemodynamic damage among preterm neonates with severe PPHN [6]. PGE1 is advantageous during neonatal transfer for infants suspected of having PPHN without DDCHD, due to oxygenation increment by PGE1 infusion and reduced deterioration during transport [49]. In addition, PGE1 treats CHD, including dextro-transposition of the arteries, among pre-term neonates with PPHN. Pre-operatively, PGE1 is utilised to control ductal patency, ensure adequate oxygenation and reduce the probability of peri-operative problems [51].

CONCLUSION(S)

PGE1 is an effective treatment for severe PPHN in newborns due to its two-fold capacity in maintaining ductal patency and promoting pulmonary vasodilation, which reduces RV stress and enhances oxygenation. It is utilised in both acute and peri-operative settings and decreases ECMO requirement among high-risk neonates. Advanced drug delivery systems have increased the efficacy of PGE1 with fewer AEs and are also considered a cost-effective option in resource-limited settings. Current and emerging literature focusing on genetics and biomarkers supports individualised PPHN management strategy development. Despite its significant role, large-scale studies and long-term follow-up are required to improve dosing.

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