Persistent Pulmonary Hypertension of the Newborn Management: Mechanistic Rationale, Comparative Evidence, and Resource-Adapted Use

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Abstract

Background: Persistent pulmonary hypertension of the newborn (PPHN) causes extrapulmonary right-to-left shunting and hypoxemic respiratory failure. Incomplete response and restricted access to inhaled nitric oxide have encouraged the use of sildenafil and magnesium sulfate.

Aim: To review the rationale, evidence, safety, and practical place of sildenafil and magnesium sulfate, alone or combined, in PPHN.

Methods: PubMed-indexed studies, Cochrane reviews, randomized trials, systematic reviews, and recent neonatal pulmonary hypertension literature available through August 2026 were synthesized, with emphasis on comparative effectiveness, administration routes, safety, and resource-limited practice.

Results: Sildenafil augments nitric oxide signaling through phosphodiesterase-5 inhibition and has the stronger evidence, particularly when inhaled nitric oxide is unavailable. Oral and intravenous formulations can improve pulmonary pressure and oxygenation, although hypotension is more frequent with intravenous treatment. Adding intravenous sildenafil to inhaled nitric oxide has not improved major outcomes. Magnesium sulfate produces nonselective vasodilation through calcium antagonism. Small studies report improved oxygenation and pulmonary pressure, but recent syntheses remain limited by heterogeneous designs and outcomes. Nebulized administration may reduce systemic effects. Combination therapy is plausible, yet evidence is insufficient for routine first-line use.

Conclusion: Sildenafil is a reasonable alternative or adjunct in selected neonates. Magnesium sulfate should remain a monitored rescue or investigational option when established therapies are inaccessible or inadequate. Treatment must be guided by lung recruitment, systemic hemodynamics, and serial echocardiography.

Keywords: persistent pulmonary hypertension of the newborn; sildenafil; magnesium sulfate; pulmonary vasodilators; neonatal intensive care

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) reflects failure of the pulmonary circulation to complete the normal fetal-to-neonatal transition. Pulmonary vascular resistance remains abnormally high, pulmonary blood flow is restricted, and deoxygenated blood crosses the patent ductus arteriosus or foramen ovale into the systemic circulation. The resulting hypoxemia may fluctuate rapidly because small changes in pulmonary or systemic vascular resistance alter the magnitude and direction of

shunting. PPHN is therefore better understood as a dynamic cardiopulmonary syndrome than as an isolated elevation in pulmonary artery pressure.[1,2]

The syndrome is encountered most often in term and late-preterm infants, although pulmonary hypertension may complicate respiratory failure in more premature neonates. Meconium aspiration, pneumonia, sepsis, perinatal asphyxia, respiratory distress syndrome, transient tachypnea, congenital diaphragmatic hernia, pulmonary hypoplasia, and idiopathic pulmonary vascular remodeling are recognized settings. The underlying phenotype influences treatment. An infant with recruitable parenchymal lung disease may improve after ventilation and surfactant, whereas an infant with severe right ventricular dysfunction requires a hemodynamic strategy that protects systemic perfusion and coronary blood flow.[2,3]

Modern management combines correction of the precipitating disorder, adequate lung inflation, avoidance of acidosis and temperature instability, selective pulmonary vasodilation, and cardiovascular support. Inhaled nitric oxide (iNO) is the best-studied pulmonary vasodilator in term and near-term infants, but approximately one-third of treated neonates show an incomplete response. Its delivery system and cost also restrict access in many neonatal units. These limitations have sustained interest in less expensive or more readily available drugs, particularly sildenafil and magnesium sulfate.[4,5]

Sildenafil enhances cyclic guanosine monophosphate (cGMP)-mediated vasodilation and is now widely used when iNO is unavailable, ineffective, or being withdrawn. Magnesium sulfate acts through broader calcium-dependent and membrane effects and has a long history of off-label use in resource-limited settings. Their different pharmacological targets offer a theoretical basis for combination treatment, yet complementary mechanisms do not by themselves establish clinical benefit. This review examines where the two agents fit within contemporary PPHN care and distinguishes encouraging physiological responses from evidence supporting meaningful neonatal outcomes.

Literature Synthesis

This focused narrative review drew on PubMed-indexed primary studies, Cochrane reviews, systematic reviews, and recent clinical reviews available through August 2026. Priority was given to evidence involving neonates with PPHN or hypoxemic respiratory failure, especially randomized comparisons, multicenter studies, route-of-administration trials, and recent quantitative syntheses. Studies of older children or chronic pulmonary arterial hypertension were used only when they clarified pharmacology or safety and were not treated as direct evidence for acute neonatal PPHN.

Transitional Circulation and Therapeutic Targets

In fetal life, the fluid-filled lung, low alveolar oxygen tension, and active vasoconstrictor pathways maintain high pulmonary vascular resistance. Pulmonary blood flow represents a limited proportion of combined ventricular output, and most right ventricular output bypasses the lungs through the ductus arteriosus. With lung aeration after birth, alveolar oxygen tension rises, mechanical compression around pulmonary vessels falls, and endothelial vasodilator pathways are activated. Pulmonary resistance decreases sharply, pulmonary flow increases, left atrial pressure rises, and fetal shunts begin functional closure.[3,4]

Nitric oxide produced by endothelial nitric oxide synthase diffuses into pulmonary arterial smooth muscle and activates soluble guanylate cyclase. The resulting rise in cGMP lowers cytosolic calcium and relaxes smooth muscle. Phosphodiesterase type 5 (PDE5) terminates this signal by degrading cGMP. PPHN is associated with impaired nitric oxide bioavailability, altered enzyme activity, oxidative stress, and increased PDE5 signaling. Sildenafil inhibits PDE5 and preserves cGMP. Its action depends partly on existing nitric oxide production, which explains both its physiological synergy with iNO and the possibility that a severely injured pulmonary endothelium may respond variably.[4,5]

The prostacyclin pathway operates through cyclic adenosine monophosphate (cAMP), while endothelin-1 and Rho-kinase pathways favor vasoconstriction. Milrinone inhibits phosphodiesterase 3, increases cAMP, and combines vasodilation with inotropic and lusitropic effects. Bosentan blocks endothelin receptors. Magnesium does not act selectively on one pulmonary signaling cascade. It reduces calcium entry, competes with calcium at membrane and intracellular sites, modulates potassium channels, and

may reduce catecholamine release. These actions relax vascular smooth muscle but can also lower systemic vascular resistance and depress neuromuscular function.[5,6]

Oxygen is itself a pulmonary vasodilator, but excessive oxygen generates reactive oxygen species that can reduce nitric oxide signaling, increase PDE5 activity, and aggravate vascular dysfunction. The aim is adequate preductal oxygenation rather than hyperoxia. Likewise, both atelectasis and overdistension raise pulmonary resistance: collapse limits alveolar oxygen delivery to adjacent vessels, while excessive distension compresses intra-alveolar capillaries. A vasodilator given before lung recruitment may therefore produce little benefit or worsen ventilation-perfusion mismatch by increasing flow toward poorly ventilated regions.[4,6]

Clinical Phenotypes and Diagnostic Assessment

PPHN may arise from maladaptation, maldevelopment, underdevelopment, or intravascular obstruction. Maladaptation accompanies acute parenchymal disease, sepsis, or asphyxia and is often reversible when oxygenation and lung volume improve. Maldevelopment describes remodeled pulmonary vessels, including idiopathic PPHN or chronic antenatal hypoxia. Underdevelopment occurs with pulmonary hypoplasia and congenital diaphragmatic hernia, where the vascular bed is anatomically reduced. Polycythemia and hyperviscosity may obstruct pulmonary microvascular flow. These categories overlap, but they help explain why one standard vasodilator sequence cannot suit every infant.[2,3]

PPHN should be suspected in a neonate with labile hypoxemia, a preductal-postductal saturation difference, or oxygen requirement disproportionate to radiographic lung disease. A small or absent saturation gradient does not exclude the diagnosis because shunting may be predominantly atrial or bidirectional. Initial assessment includes perinatal history, examination, simultaneous right-hand and lower-limb saturations, arterial blood gas analysis, chest radiography, blood pressure, infection evaluation when indicated, and prompt echocardiography. Cyanotic congenital heart disease must be excluded before pulmonary vasodilators are escalated.[4,7]

Echocardiography confirms pulmonary hypertension, defines shunt direction, estimates pulmonary pressure when a suitable tricuspid regurgitation jet is present, and evaluates right and left ventricular performance. Septal flattening or leftward bowing, right ventricular dilation, reduced tricuspid annular plane systolic excursion, a shortened pulmonary artery acceleration time, and right-to-left ductal flow support the diagnosis. No single measure is adequate in every infant. Serial, physiology-directed echocardiography is more informative than repeated pressure estimation alone because falling pressure can accompany either recovery or deteriorating right ventricular output.[7,8]

The oxygenation index, calculated from mean airway pressure, inspired oxygen fraction, and arterial oxygen tension, remains useful for grading hypoxemic respiratory failure and considering iNO or extracorporeal membrane oxygenation (ECMO). Its interpretation must account for ventilation strategy and the underlying lung lesion. Recent work also emphasizes the disease trajectory. Lack of expected improvement over several days should prompt reconsideration of pulmonary hypoplasia, alveolar capillary dysplasia, genetic disease, structural heart disease, or an uncorrected hemodynamic problem rather than indefinite addition of vasodilators.[9]

Table 1. Physiological phenotypes of PPHN and their therapeutic implications

Predominant phenotype	Typical settings	Main physiological problem	Immediate therapeutic priority
Maladaptation with parenchymal disease	Meconium aspiration, pneumonia, RDS, sepsis	Hypoxic vasoconstriction, heterogeneous aeration, V/Q mismatch	Lung recruitment, disease-specific treatment, surfactant when indicated, then selective vasodilation
Predominant vasoconstriction with relatively clear lungs	Idiopathic PPHN, perinatal stress	High PVR with extrapulmonary shunting	Exclude CHD, optimize oxygenation and systemic pressure, initiate selective vasodilator
RV dysfunction or failure	Severe PPHN of any cause	High RV afterload, reduced LV preload, impaired systemic output	Echo-guided inotropy/inodilation, preserve coronary perfusion and ductal "pop-off," cautious vasodilation
Pulmonary hypoplasia or vascular underdevelopment	CDH, prolonged oligohydramnios	Reduced vascular bed and limited recruitability	Gentle ventilation, specialized hemodynamic care, early rescue planning; expect incomplete vasodilator response
Low SVR with sepsis or vasoplegia	Neonatal sepsis, inflammatory shock	Enhanced right-to-left shunting despite pulmonary therapy	Restore systemic perfusion and treat infection; avoid unopposed systemic vasodilation

Abbreviations: CDH, congenital diaphragmatic hernia; CHD, congenital heart disease; LV, left ventricle; PPHN, persistent pulmonary hypertension of the newborn; PVR, pulmonary vascular resistance; RDS, respiratory distress syndrome; RV, right ventricle; SVR, systemic vascular resistance; V/Q, ventilation-perfusion.

Stabilization Before Pulmonary Vasodilator Therapy

Successful treatment begins with basic physiological stability. Temperature, glucose, calcium, hemoglobin, intravascular volume, and acid-base status should be assessed and corrected without unnecessary delay. Agitation, pain, hypothermia, hypoglycemia, and acidosis can increase pulmonary resistance. Routine profound sedation or paralysis is not required for every infant, but targeted analgesia and sedation may reduce hypoxemic swings in ventilated neonates. Hyperventilation and alkali-induced alkalosis are no longer favored because benefit is transient and cerebral perfusion may be impaired.[1,4]

Ventilation aims to establish functional residual capacity without volutrauma or excessive mean airway pressure. Conventional ventilation is suitable when adequate recruitment can be achieved, while high-frequency ventilation may be useful in severe heterogeneous lung disease or air-leak risk. Exogenous surfactant should be considered when parenchymal disease and surfactant inactivation contribute to respiratory failure. In term and late-preterm infants with moderate hypoxemic failure, early surfactant combined with iNO has reduced progression to ECMO or death compared with iNO alone in selected populations.[4,10]

Preductal oxygen saturation is generally kept in the low-to-mid 90s, avoiding both hypoxemia and prolonged saturation near 100%. Systemic hypotension should not be managed to an arbitrary supraphysiological target. The chosen vasoactive agent should reflect the echocardiographic pattern. Norepinephrine or vasopressin may be useful when systemic vasodilation predominates; dobutamine or low-dose epinephrine may support ventricular output; and milrinone may assist when ventricular dysfunction coexists with high pulmonary resistance, provided systemic blood pressure can tolerate its vasodilator effect. Repeated fluid boluses without evidence of low preload may worsen right ventricular dilation and hepatic congestion.[4,7]

Inhaled Nitric Oxide as the Reference Therapy

iNO reaches ventilated lung units and is rapidly inactivated by hemoglobin, producing pulmonary selectivity with comparatively little direct systemic vasodilation. In term and near-term infants with hypoxemic respiratory failure, randomized evidence shows improved oxygenation and a reduction in the combined outcome of death or ECMO, driven mainly by reduced ECMO use. Starting at 20 parts per million is customary once lung recruitment has been optimized and significant PPHN is confirmed or strongly suspected. Response should be assessed promptly through oxygenation, shunt direction,

ventricular performance, and the ability to reduce inspired oxygen.[11]

iNO is not equally effective across all phenotypes. Poor lung inflation limits delivery to the resistance vessels, and severe left ventricular dysfunction may lead to pulmonary venous congestion when pulmonary flow rises. Routine use in preterm respiratory failure has not improved survival or bronchopulmonary dysplasia, although selected preterm infants with a clearly demonstrated PPHN phenotype may receive individualized rescue therapy. Gradual weaning is important because abrupt withdrawal can cause rebound pulmonary hypertension.[4,12]

The role of sildenafil and magnesium must be judged against this background. In a unit with reliable iNO delivery and ECMO referral, neither drug should displace well-supported stabilization and iNO pathways. Their clinical value is greatest when iNO is unavailable, when response is incomplete, when rebound occurs during weaning, or when a complementary pathway is selected after echocardiographic reassessment.

Sildenafil

Mechanism and neonatal pharmacology

Sildenafil selectively inhibits PDE5, slowing cGMP degradation and amplifying nitric oxide-mediated smooth muscle relaxation. PDE5 is abundant in the pulmonary circulation and upregulated in experimental neonatal pulmonary hypertension. Sildenafil is less lung-selective than inhaled nitric oxide because systemic administration exposes the entire circulation. Its pulmonary effect may therefore be accompanied by hypotension, especially with rapid intravenous loading, low systemic vascular resistance, ventricular dysfunction, or concurrent vasodilators.[5,6]

Neonatal exposure is influenced by gestational and postnatal age, hepatic enzyme maturation, enteral absorption, critical illness, and drug interactions. Oral dosing is inexpensive and convenient but may be unreliable during shock, gut hypoperfusion, ileus, or continuous gastric drainage. Intravenous treatment avoids enteral uncertainty and permits controlled delivery, yet it produces more rapid systemic exposure. Published protocols vary, and dosing should follow an established neonatal formulary or unit guideline rather than be improvised from chronic pediatric pulmonary arterial hypertension regimens.

Evidence for efficacy

Early small trials established proof of concept. In a blinded pilot study, Baquero et al.[13] found that oral sildenafil improved oxygenation in severely hypoxemic neonates in a setting without iNO. The trial was small and conducted before current echocardiography-guided hemodynamic practice, but it stimulated subsequent research. A Cochrane review concluded that sildenafil may reduce mortality and improve oxygenation, particularly where iNO is unavailable; however, the certainty was limited by few participants, variable diagnostic criteria, and study quality.[14]

Later syntheses have generally supported improvement in oxygenation and pulmonary artery pressure, although comparisons often combine oral and intravenous routes, differing background care, and mild-to-severe disease. A 2024 network meta-analysis of 23 randomized trials involving 902 neonates ranked combined medium-dose iNO and oral sildenafil highly for efficacy and suggested a mortality advantage with oral sildenafil plus intravenous milrinone. Network rankings are useful for hypothesis generation, but many comparisons were indirect and the underlying trials were small. They do not establish one universal sequence for all PPHN phenotypes.[15]

Route-specific trials add clinically relevant nuance. Chetan et al.[16] randomized 40 infants with mild-to-moderate pulmonary hypertension to oral or intravenous sildenafil. Time to pulmonary pressure below the study threshold did not differ, but hypotension occurred in four of 20 intravenously treated infants and in none receiving oral treatment. Very sick infants requiring iNO were excluded, so the findings should not be extrapolated to severe PPHN. In contrast, the multicenter placebo-controlled trial by Pierce et al.[17] enrolled 59 neonates already receiving iNO. Adding intravenous sildenafil neither reduced treatment failure nor shortened iNO exposure; hypotension was among the common adverse events. This result argues against routine addition of intravenous sildenafil when iNO is already effective.

Recent comparative evidence supports sildenafil as a practical oral agent in lower-resource settings. Kallimath et al.[18] randomized 36 term or late-preterm neonates to sildenafil or bosentan. A 25%

reduction in pulmonary artery systolic pressure occurred sooner with sildenafil, with median times of 36 versus 96 hours, and additional vasodilators were required less often. The trial was open-label, single-center, and excluded important severe phenotypes, yet it reinforces the relative maturity of the sildenafil evidence base compared with bosentan.

Sildenafil may also be combined with a cAMP-directed agent when myocardial dysfunction or inadequate response suggests a need for complementary physiology. A randomized double-blind trial in resource-limited care found better short-term responses with milrinone plus sildenafil than with sildenafil alone, and a separate randomized trial showed that both milrinone and sildenafil could improve pulmonary pressure and oxygenation.[19,20] Combination therapy increases the possibility of systemic hypotension, so it should be driven by echocardiographic and perfusion findings rather than by oxygen saturation alone.

Safety and monitoring

The principal acute concern is systemic hypotension. Blood pressure, perfusion, urine output, lactate, oxygen requirement, and ventricular function should be followed after initiation and dose changes. Other reported events include flushing, gastrointestinal intolerance, altered platelet function, and rare hepatic abnormalities. Ocular safety has attracted attention because PDE6 is present in the retina, but a clear neonatal retinopathy signal has not been established. The increased mortality seen with higher chronic sildenafil doses in older children with pulmonary arterial hypertension should not be directly equated with short-course neonatal PPHN treatment, yet it supports avoiding unnecessary high exposure and prolonged empiric therapy.[21]

Abrupt discontinuation may permit rebound pulmonary hypertension, particularly after several days of treatment or concurrent iNO. Weaning should begin only after oxygen requirement, shunt pattern, and right ventricular function have improved. If a neonate fails to respond, escalating sildenafil without reassessing lung inflation, ventricular performance, systemic vascular resistance, and diagnosis risks treating the wrong physiological problem.

Magnesium Sulfate

Mechanistic rationale

Magnesium reduces vascular smooth muscle contraction through antagonism of calcium influx and release, modulation of membrane channels, and reduced catecholamine transmission. It may also attenuate oxidative and inflammatory signaling. These actions can decrease pulmonary vascular tone, but they are not confined to the lung. Intravenous administration can lower systemic blood pressure, reduce myocardial contractility at high concentrations, and cause respiratory or neuromuscular depression. Renal clearance makes accumulation more likely in impaired renal function.[22]

Magnesium attracted interest before iNO became widely available because it was inexpensive and familiar in neonatal practice. Early uncontrolled series described improved oxygenation and pulmonary pressure after intravenous loading followed by infusion. Abu-Osba et al.,[23] Tolsa et al.,[24] and Chandran et al.[25] reported favorable physiological responses in small cohorts with severe PPHN. These observations were important in settings with limited rescue options, but spontaneous improvement, concurrent ventilation changes, and absence of controls prevent attribution of benefit to magnesium alone.

Comparative and contemporary evidence

Uslu et al.[26] conducted a randomized comparison of intravenous magnesium sulfate and oral sildenafil. Both groups improved, but sildenafil produced a faster clinical response and shorter ventilation duration, while magnesium required serum monitoring and carried greater concern for systemic effects. This study helped move sildenafil ahead of magnesium as the more practical alternative vasodilator.

Nebulized magnesium aims to deliver vasodilator activity to ventilated lung regions while reducing systemic exposure. In a pilot randomized trial of mechanically ventilated neonates with severe PPHN, Abdelkreem et al.[27] compared nebulized with intravenous magnesium and found a greater 24-hour reduction in oxygenation index with nebulized therapy, together with more favorable systemic hemodynamics. The trial was small and used an active magnesium comparator rather than iNO or

placebo. A 2025 nonrandomized study of 40 mechanically ventilated neonates also reported better 24-hour oxygenation and lower vasoactive requirements with nebulized treatment than with intravenous administration. Allocation method, sample size, and center-specific aerosol delivery limit generalizability.[28]

Evidence syntheses have reached somewhat different conclusions because they asked different questions and included heterogeneous studies. The 2024 systematic review by Cuttone et al.[22] screened 1,233 records but found only four comparative studies. Outcomes were too inconsistent for meta-analysis, and the authors concluded that magnesium should not replace established therapy. A 2025 meta-analysis by Tang et al.[29] reported reductions in pulmonary pressure, oxygenation index, and alveolar-arterial oxygen difference, with improved arterial oxygenation. Much of the apparent benefit arose from within-patient changes and small studies, while systemic blood pressure could fall early after treatment. An earlier Cochrane review had found no eligible randomized or quasi-randomized trials, illustrating how recently the comparative literature has developed.[30] Taken together, the evidence supports biological activity but not the same level of certainty available for iNO or sildenafil.

Safety and practical limitations

Intravenous magnesium requires continuous cardiorespiratory monitoring, frequent blood pressure assessment, urine output surveillance, and measurement of serum magnesium, calcium, and renal function. Hypotension, bradycardia, diminished neuromuscular activity, respiratory depression, ileus, and feeding intolerance are clinically relevant toxicities. Concomitant sedatives, neuromuscular blockers, calcium-channel effects, renal impairment, and systemic shock increase risk. Calcium should be immediately available for clinically significant magnesium toxicity.

Nebulization may reduce systemic adverse effects, but delivery to a ventilated neonate is technically sensitive. Device type, particle size, ventilator circuit position, humidification, endotracheal tube diameter, respiratory pattern, and lung aeration influence the deposited dose. A nominal nebulizer dose is not equivalent to pulmonary deposition. Until delivery protocols and pharmacokinetics are standardized, nebulized magnesium should be used only within an experienced protocol with careful physiological monitoring.

Sildenafil and Magnesium Sulfate Combination Therapy

Combining sildenafil with magnesium is attractive because the drugs act at different levels. Sildenafil preserves cGMP signaling, whereas magnesium reduces calcium-dependent smooth muscle contraction more broadly. In principle, magnesium could produce early relaxation while sildenafil sustains nitric oxide-related vasodilation. Combination therapy may also allow lower exposure to either drug. The opposing concern is additive systemic vasodilation, particularly in sepsis, myocardial dysfunction, or low left ventricular preload.

Huang and Zhong[31] reported a randomized study of 174 neonates in which sildenafil plus magnesium was associated with better pulmonary hemodynamic and inflammatory measures than sildenafil alone. Another Egyptian comparative study published in 2024 also reported favorable physiological outcomes with combined treatment relative to either agent alone.[32] These findings are encouraging, but the evidence remains geographically concentrated, outcome definitions differ, and independent replication is limited. Neither trial establishes superiority for mortality, ECMO avoidance, neurodevelopment, or other long-term outcomes.

The combination should therefore not be presented as a standard replacement for iNO. A defensible role is rescue therapy in a closely monitored neonatal intensive care unit when iNO is unavailable and sildenafil alone has produced an incomplete response, or when a local protocol is supported by experienced echocardiography and laboratory monitoring. Before adding magnesium, clinicians should confirm adequate lung recruitment, exclude pulmonary venous hypertension and structural heart disease, assess systemic vascular resistance, and ensure renal function and blood pressure can tolerate nonselective vasodilation.

Table 2. Selected clinical evidence for sildenafil and magnesium sulfate in neonatal PPHN

Study	Design and population	Comparison	Main finding	Key limitation
Baquero et al., 2006[13]	Pilot randomized blinded trial; severe PPHN without iNO access	Oral sildenafil vs placebo	Sildenafil improved oxygenation and suggested survival benefit	Very small sample and older supportive-care context
Pierce et al., 2021[17]	Multicenter double-blind RCT; 59 neonates receiving iNO	IV sildenafil vs placebo added to iNO	No reduction in treatment failure or iNO duration	Tested add-on therapy, not sildenafil where iNO was unavailable
Chetan et al., 2022[16]	Open-label RCT; 40 neonates with mild-to-moderate PH	Oral vs IV sildenafil	Similar pressure response; hypotension occurred in 4/20 IV-treated infants	Severe PPHN requiring iNO was excluded
Kallimath et al., 2024[18]	Open-label RCT; 36 term/late-preterm neonates	Oral sildenafil vs bosentan	Faster 25% PASP reduction and less rescue therapy with sildenafil	Single center, small sample, selected phenotype
Uslu et al., 2011[26]	Randomized trial	IV magnesium vs oral sildenafil	Both improved; sildenafil produced faster clinical response	Limited sample and nonuniform outcome reporting
Abdelkreem et al., 2021[27]	Pilot RCT; ventilated severe PPHN	Nebulized vs IV magnesium	Nebulized route showed greater OI improvement and better hemodynamic profile	Small active-comparator trial; no iNO or placebo arm
Mohamed et al., 2025[28]	Nonrandomized controlled study; 40 ventilated neonates	Nebulized vs IV magnesium	Better 24-hour oxygenation and lower vasoactive requirement with nebulization	Nonrandom allocation and single-center delivery protocol
Huang and Zhong, 2021[31]	Randomized study; 174 neonates	Sildenafil plus magnesium vs sildenafil	Combination improved short-term hemodynamic and laboratory outcomes	Limited external replication and no long-term outcome evidence

Abbreviations: iNO, inhaled nitric oxide; IV, intravenous; OI, oxygenation index; PASP, pulmonary artery systolic pressure; PH, pulmonary hypertension; PPHN, persistent pulmonary hypertension of the newborn; RCT, randomized controlled trial.

Other Adjunctive and Rescue Therapies

Milrinone is useful when PPHN is accompanied by right or left ventricular dysfunction, low cardiac output, or inadequate response to iNO. By increasing cAMP, it can improve myocardial performance and lower pulmonary resistance, but systemic hypotension may require concurrent vasopressor support. Bosentan has shown mixed results. In the FUTURE-4 trial, it was well tolerated as adjunctive treatment but did not improve oxygenation or clinical outcomes when added to iNO.[33] Prostacyclin analogues can be delivered intravenously or by inhalation in refractory disease, although neonatal evidence is largely observational and systemic hypotension or ventilation-perfusion effects require caution.

Prostaglandin E1 may be beneficial in selected severe PPHN with right ventricular failure by maintaining ductal patency as a pressure-relief pathway. A recent cohort described improved right ventricular function and oxygenation after prostaglandin E1 initiation in critically ill neonates.[34] This is a physiology-specific intervention, not a general vasodilator substitute, and should be guided by expert echocardiography. ECMO remains the definitive rescue for refractory hypoxemic respiratory or circulatory failure in eligible infants when maximal conventional treatment is insufficient.

A Resource-Adapted Treatment Framework

Resource constraints alter available choices but do not change the physiological priorities. In every setting, treatment starts with recognition of the underlying disease, effective ventilation, adequate but not excessive oxygen, correction of acidosis and metabolic disturbance, circulatory assessment, and echocardiographic exclusion of congenital heart disease. Sildenafil should not be used as a substitute for lung recruitment or systemic resuscitation.

Where iNO is available, a term or near-term infant with moderate-to-severe hypoxemic respiratory failure and confirmed PPHN should generally receive iNO after recruitment and hemodynamic assessment. Sildenafil may be added for incomplete response, difficulty during iNO weaning, or a complementary cGMP strategy, but the negative add-on trial of intravenous sildenafil cautions against automatic combination. If ventricular dysfunction is prominent, milrinone may be more rational than adding another predominantly vasodilator drug.

Where iNO is unavailable, oral sildenafil has the strongest balance of evidence, feasibility, and cost among commonly used alternatives. Treatment should begin under continuous monitoring with serial assessment of oxygenation, systemic pressure, perfusion, and echocardiography. Intravenous sildenafil is an option when enteral absorption is unreliable, but the higher risk of hypotension requires particular caution. Magnesium sulfate may be considered only when sildenafil is unavailable, contraindicated, or insufficient and when serum monitoring, renal assessment, and toxicity management are feasible.

Table 3. Practical monitoring during sildenafil or magnesium therapy

Domain	Sildenafil	Magnesium sulfate	Action if deterioration occurs
Systemic hemodynamics	Continuous HR and saturation; frequent BP; perfusion, urine output, lactate	Same, with heightened concern for nonselective vasodilation	Pause escalation; reassess SVR, preload, ventricular function, sepsis, and concurrent vasoactive drugs
Respiratory status	FiO_2, OI or OSI, ventilator pressure, pre/postductal saturation	Same; observe for respiratory or neuromuscular depression	Confirm tube position and lung recruitment; exclude pneumothorax and worsening parenchymal disease
Echocardiography	Shunt direction, RV/LV function, septal position, pressure estimates	Same	Do not interpret pressure alone; distinguish recovery from falling RV output
Laboratory surveillance	Hepatic function when prolonged; drug interactions	Serum magnesium and calcium, creatinine, urine output	Stop or reduce therapy if accumulation or toxicity develops; treat significant toxicity promptly
Treatment course	Avoid abrupt withdrawal after sustained therapy	Avoid prolonged infusion without documented response	Wean only after stable oxygenation and improving echo physiology; reconsider diagnosis if response is absent

Abbreviations: BP, blood pressure; FiO_2, fraction of inspired oxygen; HR, heart rate; LV, left ventricle; OI, oxygenation index; OSI, oxygen saturation index; RV, right ventricle; SVR, systemic vascular resistance.

Evidence Gaps and Research Priorities

Most neonatal vasodilator trials are small, single-center, and heterogeneous. Diagnostic thresholds vary, echocardiographic measures are not standardized, and infants with different etiologies are frequently analyzed together. Oxygenation can improve rapidly as the underlying lung disease resolves, making uncontrolled before-and-after studies particularly vulnerable to overestimating drug effect. Future trials should use core outcome sets that include treatment failure, time to stable low oxygen requirement, ventilator-free days, ECMO, mortality, systemic hypotension, cerebral and renal safety, hearing, and neurodevelopment.

Phenotype-stratified enrollment is equally important. Trials should distinguish parenchymal PPHN with recruitable lung disease from idiopathic vasoconstriction, ventricular dysfunction, sepsis-associated vasoplegia, congenital diaphragmatic hernia, and pulmonary hypoplasia. Serial echocardiography should document not only pressure but also right ventricular-pulmonary arterial coupling, ventricular

output, shunt direction, and response to treatment. Pharmacokinetic studies are needed for oral and intravenous sildenafil across gestational ages and for nebulized magnesium under neonatal ventilation conditions.

The most clinically useful magnesium trial would compare a standardized nebulized regimen with the best locally available treatment, using concealed randomization and blinded outcome assessment. For combination therapy, adequately powered multicenter studies should compare sildenafil alone with sildenafil plus magnesium in settings without iNO, while prespecifying systemic hypotension and long-term outcomes. Cost-effectiveness also matters. Sildenafil may be economically attractive where iNO infrastructure is absent, but safe treatment still requires trained staff, echocardiography, monitoring, and referral pathways.[35]

Conclusion

Sildenafil and magnesium sulfate address an important therapeutic gap in neonatal units where iNO is unavailable or insufficient. Sildenafil has the more coherent mechanism-specific and clinical evidence base and is a reasonable alternative in carefully selected neonates, especially in resource-limited care. Intravenous treatment is useful when enteral delivery is unreliable but demands close surveillance for hypotension. Magnesium sulfate has demonstrable pulmonary vasodilator activity, and nebulized delivery is promising, yet available studies remain too heterogeneous to support routine first-line use. Combining sildenafil with magnesium is biologically plausible and supported by limited short-term studies, but superiority for major neonatal outcomes has not been established. The safest approach remains physiology-directed: recruit the lung, treat the cause, protect systemic perfusion, define ventricular function, and use serial echocardiography to select and reassess therapy.

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