BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-087740
Article Type:	Original research
Date Submitted by the Author:	21-Apr-2024
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Keywords:	NEONATOLOGY, PAEDIATRICS, Pulmonary Disease < Lung Diseases

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Scoping review of initiation criteria for inhaled nitric oxide in preterm infants after 7 days of age

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ABSTRACT

Objectives: Inhaled nitric oxide (iNO) is a known treatment for pulmonary hypertension (PH) associated with bronchopulmonary dysplasia in preterm infants after 7 days of age (post-acute phase). However, a consensus regarding the optimal criteria for initiating iNO therapy in this population in the post-acute phase is currently lacking. This study therefore aimed to identify the criteria for initiating iNO therapy, alongside the associated clinical and echocardiographic findings, in this population.

Design: We performed a scoping review using the population–concept–context framework following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.

Data sources: The PubMed, Embase, and the Japanese database "Ichushi" were systematically searched for relevant articles published between January 2003 and August 2023.

Eligibility criteria: This study included randomized controlled trials, prospective and retrospective cohort studies, case-control studies, and case series on iNO therapy in the post-acute phase for preterm infants born before 34 gestational weeks, written in English or Japanese.

Data extraction and synthesis: Data screening, extraction, and charting were performed independently, with the characteristics and findings of the included studies subsequently summarized.

Results: We included 14 reports that analyzed the data of 12 separate studies. The utilization of iNO therapy was categorized as prophylactic, rescue, or other modalities. While randomized controlled trials and retrospective analyses indicated the safety of iNO during the post-acute phase, the latter highlighted poor prognoses associated with severe cases requiring rescue iNO therapy. Additionally, although echocardiography is currently the primary diagnostic tool for identifying PH in preterm infants, standardized diagnostic criteria are lacking. Further, reports of complications and side effects associated with iNO are rare.

Conclusion: Our exploration of the initiation criteria for iNO revealed that definitive guidelines have not been established. Nonetheless, iNO administration during the post-acute phase appeared to be safe and devoid of complications.

Trial registration number: UMIN000051498.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This scoping review is the first to provide a comprehensive overview of the use of inhaled nitric oxide therapy in preterm infants during the post-acute phase.

- To ensure transparency, this review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.
- We conducted a thorough search across three databases, including the Japanese database "Ichushi,'' where the most vulnerable preterm newborns with a history of active resuscitation for years, have been documented.
- A quality assessment of the included studies was not performed in this review, as it was beyond the scope of this study's objectives.

INTRODUCTION

Nitric oxide (NO) is a gaseous agent with a targeted effect on pulmonary hypertension (PH), significantly improving outcomes in newborns.[1, 2] In the United States, medical insurance limitations restrict the use of NO before 34 weeks of postmenstrual age. However, experience with inhaled NO (iNO) treatment has accumulated globally, with reports detailing its effect on both short- and long-term prognoses in premature newborns.[3, 4, 5] Bronchopulmonary dysplasia (BPD) significantly impacts pulmonary function and neurodevelopmental outcomes in premature newborns, with studies indicating that newborns with moderate-to-severe BPD may develop hypoxic respiratory failure (HRF) or PH in the post-acute phase, which can be potentially fatal.[6, 7]

Notably, the efficacy of iNO during the post-acute phase has been documented for both BPD prevention and rescue from HRF or PH.[8, 9, 10] However, its effectiveness remains suboptimal. For example, iNO is not covered by medical insurance when initiated after the first week of life in Japan. Hence, it is imperative to establish evidence supporting its efficacy and broaden its indications to include the post-acute phase.

Despite the increasing off-label use of iNO, the criteria for its initiation vary across studies. Neonatologists have utilized diverse parameters to diagnose hypoxia, including oxygen saturation, arterial oxygen partial pressure, and the oxygenation index.[11, 12, 13] Similarly, various echocardiographic findings are used to diagnose PH.[7, 14] Echocardiography is considered the gold standard for PH diagnosis in newborns; however, logistical challenges may hinder its implementation prior to the initiation of iNO treatment in certain countries. Indeed, iNO is sometimes employed for clinical HRF or PH in the absence of any definitive echocardiographic findings, partly because of the aforementioned reasons. We believe that the current perceived inadequacy of post-acute iNO therapy may be partly due to the enrollment of heterogeneous populations without a robust diagnosis of PH in prior studies investigating iNO efficacy.[15] In addition, while the mechanism of action of iNO renders it suitable for PH treatment, the optimal initiation criteria, particularly among premature infants in the post-acute phase, remain unclear.

Presently, there is a dearth of comprehensive information regarding the actual usage and initiation criteria for post-acute iNO in Japan and other nations. This review, therefore, aimed to provide a comprehensive overview of existing evidence concerning the initiation criteria for iNO administration after 7 days of life, along with any pertinent associated information.

METHODS AND ANALYSIS

Protocol and registration

The protocol of this scoping review was registered at UMIN-CTR (registration number: UMIN000051498), and was subsequently published.[16] This review was conducted in compliance with the published protocol.

Eligibility criteria

This scoping review followed the Population-Concept-Context (PCC) framework outlined by the Joanna Briggs Institute (Table 1, https://doi.org/10.46658/JBIMES-20-12). Articles meeting the following eligibility criteria were included: (1) articles enrolling preterm infants born at <34 weeks of gestation and aged >7 days; (2) provision of clinical information on iNO usage; (3) publication between January 2003 and August 2023; (4) conducted in developed countries; (5) written in English or Japanese; and (6) encompassing study designs such as

randomized controlled trials (RCTs), prospective and retrospective cohort studies, case-control studies, and case series. The exclusion criteria were as follows: (1) participants with congenital malformation syndrome or chromosomal abnormalities; (2) animal and in vitro studies; and (3) conference abstracts, trial registrations, and protocol publications.

Table 1. PCC framework of this scoping review

Population	Preterm infants born at <34 weeks of gestation and treated with iNO after 7 days of age
Concept	Aim to identify the initiation criteria of iNO, postnatal day of the iNO initiation, dosage of iNO (ppm), duration of iNO therapy, discontinuation criteria of iNO therapy, concomitant use of other drugs, and adverse effects
Context	Published between January 2003 and August 2023 Conducted in developed countries Published in English or Japanese Randomized controlled trial, cohort study, case-control study, and case series

Excluding congenital malformation syndrome and a chromosomal abnormality

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PCC, Population-Concept-Context; iNO, inhaled nitric oxide

Information sources

We conducted searches across PubMed and Embase, as well as the Japanese electronic bibliographic database "Ichushi." These searches were carried out by an accomplished librarian, supplemented by manual searches conducted by the authors. Given the paradigm shift in BPD to "new BPD" highlighted by Jobe in 1999,[17] alongside the advent of iNO in the clinical neonatology domain around 2000, we limited our search to studies published within the most recent two decades, spanning from January 2003 to August 2023. The search strategies are detailed in the Supplemental Appendix.

Selection of sources of evidence

Our scoping review approach adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist.[18] The search results were deduplicated using EndNote 20, and imported into Rayyan, a web application,[19] to screen eligible studies. The authors (YM, MH, TN, and SI) independently evaluated the titles and abstracts of the identified studies using the PCC framework to ascertain potential eligibility based on the inclusion criteria. Subsequently, a thorough full-

text review of potentially eligible studies was performed. Any discrepancies regarding study eligibility were resolved through consensus discussion among the authors or adjudicated by another author's (SK) assessment. The study selection process is illustrated in the PRISMA flow diagram in Figure 1.

Data charting and synthesis of results

The characteristics of the included studies, including the study design, settings, populations, information regarding the provision of iNO therapy, efficacy of iNO therapy, complications, and other relevant findings, were systematically summarized in a pre-designed Excel form (Tables 3 and 4).

Critical appraisal of individual sources of evidence

Given the overarching objective of this scoping review to map existing evidence, an assessment of the risk of bias within the included studies was not undertaken.

Patient and public involvement

This study did not involve patients or members of the public, as only existing articles were analyzed. However, neonatologists participated in the review process and discussed the results.

RESULTS

Selection of sources of evidence

A literature search was conducted on February 1, 2024, yielding 1518 records. Following deduplication, 393 duplicate records were removed. Subsequently, the remaining 1125 records underwent title and abstract screening, resulting in the exclusion of 999 records that did not meet the inclusion criteria. A full-text review of the remaining potentially eligible studies was subsequently performed, leading to the exclusion of an additional 107 citations. Notably, one relevant Japanese study published in 2012 was identified through a manual literature search and included in the review. Ultimately, 18 original records were included in this study.

Characteristics and results of sources of evidence

Studies investigating prophylactic iNO use for BPD

Three RCTs investigated the use of iNO administration to prevent the development of BPD.[8, 9, 11] All of these studies were multicenter and involved a relatively large number of patients, ranging from 451 to 582. The findings of these included studies are summarized in Table 2.

Table 2. Summary of the findings of the included studies

	Author Year	Study design	Country	Setting	Population	Intervention or Concept	Study findings
Studies investigating prophylactic iNO use for BPD							
1	Ballard et al. 2006[8]	RCT	USA	Multicenter (21 centers)	GA; ≤32 weeks BW; 500–1250 g on MV Treatment; 7 and 21 days of age (n=582).	iNO: n=294 N_2: n=288	Survival without BPD; 43.9% in NO and 36.8 % placebo (RB: 1.23, 95% CI: 1.01–1.51, P=0.042) iNO group discharged sooner (P=0.04), shorter supplemental oxygen use (P=0.006). There were no short-term safety concerns and no difference in the complications of prematurity.
2	Ballard et al. 2016[11]	RCT	USA	Multicenter (25 centers)	GA; ≤28 weeks on MV Treatment; 7 and 14 days of age (n=511)	iNO+surfactant: n=252 iNO only (control): n=259	Survival without BPD; 36 weeks, 31.3% vs. 33.7%, RB: 0.98, (95% CI: 0.75–1.28 P=0.89); 40 weeks, 58.7% vs. 54.1%, RB: 1.08 (95% CI: 0.92–1.27 P=0.33). There was no difference in serious adverse events, comorbidities of prematurity, and the severity of lung disease @ 36 weeks.

							Survival without BPD was not improved at 36 weeks.
3	Hasan et al. 2017[9]	RCT	Canada	Multicenter (33 centers)	GA; <30 weeks Treatment; 5–14 days of age (n=451)	iNO: at 7 and 14 days of age iNO: n=175 N_2: n=175	Respiratory and neurodevelopmental outcomes were not different at 18–24 months of postmenstrual age. There was no difference in the common complications of prematurity.
Studies investigating rescue iNO use for PH							
4	Truog et al. 2014[10]	Retrospective cohort	USA	Multicenter (13 centers)	GA; <29 weeks, BW; 400–1000 g (n=187)	iNO started at ≥7 days of age	iNO administration between days 7 and 14 was associated with an increased risk of BPD or death (OR: 2.24, 95%CI: 1.23–4.07) No information regarding complications or adverse events of iNO use was reported.
5	Hsiao et al. 2019[20]	Retrospective cohort	Taiwan	Single tertiary center	GA; 30.5 (26.0–36.5) weeks, BW; 1305 (788.5–2532) g, (n = 27)	Off-label use of iNO as "final rescue" for refractory hypoxemia (not for PPHN)	Common causes of off-label iNO use included BPD (19/27, 70.4%) and secondary PH (14/27, 51.9%) The Off-label iNO use group demonstrated the poorest response and the highest in-hospital mortality (P <0.001).

6	Nakanishi et al. 2023[4]	Retrospective cohort	Japan	Multicenter (NRNJ database)	GA; <28 weeks (n=462)	Post-acute iNO (iNO use in the late phase of hospitalization without PPHN)	Post-acute iNO use increased in extremely preterm infants with more severe disease and complications. Post-acute iNO was not associated with long-term neurodevelopmental outcomes at 3 years of age. No adverse events that could be related to iNO therapy were reported.
7	Oka et al. 2023[13]	Retrospective cohort	Japan	Single tertiary center	GA; <28 weeks, BW; 620 (482–814) g, (n=30)	iNO after 96 h of age (not for PPHN)	There was no difference in in-hospital outcomes between responders and non-responders. Methemoglobinemia (MetHb >5%) did not occur in any participant. Early iNO was associated with treatment response (OR: 0.89, 95% CI: 0.7970–0.995; P=0.04)
8	Fraga et al. 2023[14]	Prospective cohort	USA	Single tertiary center	GA; 25 weeks (24–27), (n=37)	iNO used at cGA ≥36 weeks, 40 weeks (37–43) at study entry (n=37)	Thirty (81%) patients had echocardiographic evidence of PAH before iNO, and 19 (56%) after 48 h of iNO (P=0.04). FiO_2 requirements were significantly different between time points, before

							initiation of iNO and after 48–168 h (P=0.05)
9	Nakao et al. 2012[21]	Retrospective cohort	Japan	Single tertiary center	GA; 24 weeks (22–28) BW 507.5 g (320–710 g) (n=12)	iNO used at ≥ 7 days	Indication HRF with PH (n=10), CLD with PH (n=3) Outcome Death (n=8) No complications were reported Background Historical CAM (n=9), SGA (<-3 SD) (n=2)
10	Iwatani et al. 2022[22]	Retrospective cohort	Japan	Multicenter (10 centers)	GA; <28 weeks (23–27), BW; 417–1070 g (n=12)	iNO used at ≥ 7 days	Indication CLD with PH (n=7), HRF with PH (n=5) Outcome Death (n=8), HOT (n=3), tracheostomy (n=1)
Other studies							
11	Athvale et al. 2004[23]	Prospective cohort	USA	Single center	A total of 13 ventilated preterm infants with BW of 500–1500 g (n=13)	To evaluate the acute effects of low-dose iNO in preterm infants with evolving BPD	iNO did not affect lung compliance, pulmonary resistance, or N_2 clearance. There was a small increase in LVEF (P<0.05). Mean SpO_2 remained unchanged, but the duration of spontaneous hypoxemic episodes increased during iNO (P<0.05).

12	Di Fiore et al. 2007[24]	RCT	USA	Multicenter (21 centers)	Ventilated preterm infants with GA of 24. 9 (24–27) weeks and BW of 500–1250 g (n=71)	iNO; n=34 placebo; n=37 for ≥ 24 days at 7–21 days of life	There is no effect of NO on expiratory resistance or compliance after 1 h, 1 week, 2 weeks of gas administration.
13	Hibbs et al. 2008[25]	RCT	USA	Multicenter (21 centers)	GA; ≤32 weeks BW; 500–1250 g on MV Treatment; 7 and 21 days of age (n=582).	iNO: n=230 N_2: n=225	Infants randomized to iNO had less pulmonary medication use (bronchodilators, OR: 0.53 [95% CI: 0.36–0.78]; systemic steroids, OR: 0.56 [0.32–0.97]; diuretics, OR: 0.54 [0.34–0.85]; supplemental oxygen, OR: 0.65 [0.44–0.95]) than infants randomized to placebo at the 12-month follow-up
14	Hussain et al. 2022[12]	Before–after study	USA	Single center	Before; 32.2±6.5 After; 33.8 ±6.6 (n=67)	Comparing a retrospective control group to a prospective cohort after implementation of an iNO weaning protocol	The implementation of an iNO weaning protocol significantly decreased iNO usage by approximately 60% (149 h [IQR, 63–243] vs. 59 h [37–122]) (P=0.008)

iNO, inhaled nitric oxide; GA, gestational age; BW, birth weight; RB, relative benefit; CI, confidence interval; OR, odds ratio; BPD, bronchopulmonary dysplasia; RCT, randomized controlled trial; PH, pulmonary hypertension; HRF, hypoxic respiratory failure; LVEF, left ventricular ejection fraction; NRNJ, Neonatal Research Network of Japan; IQR, interquartile range; PAH; pulmonary artery hypertention, CLD; chronic lung disease, CAM; chorioamnionitis, SGA; small for gestational age, HOT; home oxygen therapy, LVEF; left ventricle ejection fraction, PPHN; persistent pulmonary hypertention of the newborn, MV; mechanical ventilation

All studies included in the analysis investigated survival without BPD as the primary outcome. Among them, only one study showed the efficacy of iNO within the treated group (relative benefit: 1.23, 95% confidence interval: 1.01–1.51, P=0.042),[8] while the remaining studies did not demonstrate improvement.[9, 11] None of the studies reported an increase in short-term outcomes or prematurity-associated comorbidities. Additionally, it is worth mentioning that although the study by Hasan enrolled newborns between 5 and 14 days of age, it did not specify when iNO therapy was initiated. Nevertheless, we included this study as it yielded significant findings, demonstrating no difference in respiratory or neurodevelopmental outcomes at 18 to 24 months postmenstrual age.[20]

Studies investigating rescue iNO use for HRF and PH

Seven studies focused on the use of iNO for rescue purposes. These studies comprised two database analyses,[4, 10] four retrospective cohort studies conducted in single tertiary centers,[13, 14, 20, 21] and one multicenter retrospective cohort study.[22] Additionally, we included two retrospective reports in Japanese, and summarized their results by extracting patient information that matched the study concept provided by the authors.[21, 22] The number of participants ranged from 12 to 462. A summary of these studies is presented in Table 2. Among these studies, four reported worse respiratory outcomes, and four reported death before discharge. Oka et al.[13] noted a positive response to post-acute iNO, defined as a >20% reduction in the oxygen saturation index (OSI), when introduced earlier. They also found no difference in the

incidence of in-hospital outcomes between responders and non-responders. Despite finding that two newborns received iNO treatment on day 6 of life and another on day 5, we included this study as the majority of the included newborns matched the inclusion criteria. Nakanishi et al.[4] reported in their retrospective cohort study using the Neonatal Research Network of Japan (NRNJ) database that there was no increase in developmental outcome at 3 years of age following post-acute iNO treatment. Fraga et al.[14] emphasized the importance of echocardiographic assessment of PH in infants with severe BPD before initiating iNO.

Other studies

Four studies were included in the analysis, despite not completely aligning with our research concept, as they still provided valuable information. These included two multicenter RCTs,[24, 25] one prospective cohort study conducted in a tertiary center,[23] and a before-and-after comparison study.[12] Additionally, two secondary follow-up analyses of a previous RCT were incorporated. The participant numbers ranged from 13 to 582.

Among these studies, three included very-low-birth-weight infants as an inclusion criterion,[23, 24, 25] while one included preterm infants.[12] Table 2 provides a summary of the included studies. This subgroup comprised two reports on respiratory function,[23, 24] one on respiratory prognosis at 1 year of age,[25] and one on a quality improvement (QI) project aimed at reducing inappropriate iNO use.[12]

Synthesis of results

Initiation criteria for post-acute iNO

The diagnostic criteria for PH are poorly described, and may not be crucial for post-acute iNO use. Among three studies focusing on iNO prophylaxis for BPD, none reported the diagnostic criteria for PH due to the nature of the studies.[8, 9, 11] However, in five studies examining the use of echocardiography to diagnose PH before iNO initiation, various criteria were reported.[12, 13, 14, 20, 22] Specifically, four studies identified ventricular septal wall flattening or bowing in the end-systole or pulmonary artery (PA) pressure elevation as indicators of PH.[12, 13, 14, 22] Fraga et al. further provided additional detailed echocardiographic findings for PH diagnosis, such as right-to-left shunting at the patent foramen ovale (PFO) or patent ductus arteriosus (PDA) level and the tricuspid peak velocity (TPV):right ventricular ejection time (RVET) ratio, as markers for PA pressure (PAP) elevation.[14] To measure the severity of respiratory compromise, various measures have been utilized. Four studies employed the respiratory severity index (mean airway pressure [MAP] × fraction of inspired oxygen [FiO_2]),[8, 11, 12, 25] one utilized the OSI,[13] and two employed the oxygenation index.[12, 21] In out-of-concept studies, Hussein et al. reported the use of echocardiography for PH diagnosis and noted echocardiographic findings, including flattened ventricular septum, tricuspid regurgitation (TR), and right-to-left shunt at the PFO/PDA level.[12] They also reported a 60% reduction in iNO use following the implementation of a weaning protocol.

A summary of these findings is presented in Table 3.

Table 3. Initiation criteria for iNO in all of the included studies

	Author	Initiation criteria for iNO			
		PH diagnosis	Echocardiographic findings	Surrogate marker of disease severity	Others
1	Ballard et al. 2006	N/A	N/A	MAP×FiO_2	N/A
2	Ballard et al. 2016	N/A	N/A	MAP×FiO_2	N/A
3	Hasan et al. 2017	N/A	N/A	N/A	N/A
4	Truog et al. 2014	N/A	N/A	N/A	N/A
5	Hsiao et al. 2019	Echocardiography	Details were not available	N/A	N/A
6	Nakanishi et al. 2023	N/A	N/A	N/A	N/A
7	Oka et al. 2023	Echocardiography (24%)	TR (PA>40 mmHg) D-shaped LV	OSI = MAP×FIO_2×100 /SpO_2	N/A
8	Fraga et al. 2023	Echocardiography	RV pressure >½ sSBP estimated from TRJV. Bidirectional or right-to-left shunting through a PDA. Septal flattening or bowing at end-systole. TPV:RVET ratio, 0.2–0.3, moderately elevated PAP; ≤0.2, significantly elevated PAP.	N/A	N/A

9	Nakao et al. 2012	N/A	N/A	Oxygenation index	N/A
10	Iwatani et al. 2022	Cyanosis echocardiography	TR D-shaped LV	N/A	N/A
11	Athavale et al. 2004	N/A	N/A	N/A	N/A
12	Fiore et al. 2007	N/A	N/A	N/A	N/A
13	Hibbs et al. 2008	N/A	N/A	MAP×FiO_2	N/A
14	Hussain et al. 2022	Defined as HRF with signs of pulmonary hypertension on an echocardiogram dictated by a pediatric cardiologist.	・Leftward bowing of the interventricular septum ・Tricuspid regurgitation ・Right-to-left or bidirectional shunting at the levels of the patent foramen ovale and patent ductus arteriosus	Oxygenation index, respiratory severity score (FiO_2×MAP)	Eligibility for weaning iNO: iNO ≤20 ppm, FiO_2 ≤60%, PaO_2 ≥60 mmHg, SpO_2 ≥90%

OSI, oxygen saturation index; pulmonary artery; TPV, tricuspid peak velocity; RVET, right ventricular ejection time; PAP, pulmonary artery pressure; MAP, mean airway pressure; FiO_2, fraction of inspired oxygen; TR, tricuspid regurgitation; iNO, inhaled nitric oxide; RV, right ventricle; LV, left ventricle; sSBP, systolic systemic blood pressure; PaO_2, partial pressure of oxygen; SpO_2, peripheral oxygen saturation; TRJV, tricuspid regurgitant jet velocity; HRF, hypoxic respiratory failure

Details of post-acute iNO administration

The starting dose of iNO ranged from 3–20 ppm, with six studies starting at 20 ppm[8, 9, 11, 20, 24, 25], and one study reporting a maximum dose of 80 ppm.[20] The duration of iNO administration varied widely, ranging from 2 to 314 days. The extended duration of iNO treatment may be attributed to its utilization as a rescue therapy in post-acute cases. Notably, five RCTs included a 24-day pre-protocol dosing period.[8, 9, 11, 24, 25] Regarding adjunctive medications, reports involving the use of surfactants,[11, 13, 20] inotropes,[12, 20] corticosteroids[13], bronchodilators[14], and diuretics[14] were included. RCTs did not report significant differences in adverse events or increases in complications related to preterm birth,[8, 9, 11, 24, 25] which aligns with the findings of retrospective studies.[4, 12, 13, 21, 22, 23] However, one case of pulmonary edema was reported after 48–168 h of iNO administration, without evidence of left ventricle dysfunction based on echocardiography.[14] A summary of these data is presented in Table 4.

Table 4. Summary of the details of post-acute iNO administration in preterm infants in the included studies

	Author Year	Postnatal day of iNO initiation	Dosage of iNO (ppm)	Duration of iNO	Other drugs	Adverse effects
1	Ballard et al. 2006	7–21 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	N/A	No difference in the complications of prematurity No methemoglobinemia
2	Ballard et al. 2016	7–14 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	Surfactant	No difference in severe adverse events and complications of prematurity
3	Hasan et al. 2017	7–14 days	Start with 20 ppm Decreased to 10 ppm in 72–96 h Then 5 ppm on day 10 or 11 Remain at 5 ppm until completion of therapy for 24 days	Minimum 24 days	N/A	No differences in common complications of prematurity No elevation in NO_2 or methemoglobin level
4	Truog et al. 2014	7–28 days: (n=140 or 2.9%) >28 days:	N/A	N/A	N/A	N/A

		(n=47 or 0.96%)				
5	Hsiao et al. 2019	> 7 days	Start with 20 ppm (rarely 10 ppm) Increased to 40 ppm without clinical response (max 80 ppm)	N/A	Surfactant 17 (3.7%) Dopamine 27 (37.0%) Dobutamine 27 (22.2%) Epinephrine 27 (11.1%) Milrinone 27 (22.2%)	N/A
6	Nakanishi et al. 2023	N/A (post-acute iNO; defined as iNO administration in the late phase of hospitalization)	N/A	26 days [14–70 days]	N/A	N/A
7	Oka et al. 2023	19 (11–26) days	Starting dose: 10 ppm	20.5 (8–32.5) days	Surfactant corticosteroids	No complications No methemoglobinemia
8	Fraga et al. 2023	40 weeks (37–43)	20 ppm	N/A	Bronchodilators; n=16 (43%)	Pulmonary edema; n=1

					Diuretics; Furosemide: n=15 (40%) Chlorothiazide: n=16 (43%)	
9	Nakao et al. 2012	>7 days (214–2880 h)	Starting dose: 3–20 ppm Highest dose: 5–40 ppm	Median 130 h (22–1330 h)	N/A	No complications
10	Iwatani et al. 2022	39 (12–142) day	N/A	2–36 days	N/A	No methemoglobinemia No jaundice
11	Athvale et al. 2004	32.1 (16–55) days	10 ppm	2 h	N/A	No changes in head ultrasonography after the study
12	Fiore et al. 2007	7–21 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	N/A	N/A
13	Hibbs et al. 2008	7–21 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	N/A	N/A

14	Hussain et al. 2022	Before; 36.4±8.4 weeks After; 35.2 ±6.3 weeks	Starting dose: 10 ppm Highest dose: 20 ppm	Before: 149 (63–243) h After: 59 (37–122) h	Sildenafil, n (%) 8 (22) vs. 2 (6) P=0.09 Milrinone, n (%) 16 (43) vs. 15 (50) P=0.58 Epoprostenol, n (%) 6 (16) vs. 3 (10) P=0.45	No notable negative effects

iNO, inhaled nitric oxide

DISCUSSION

Summary of evidence

In this scoping review, a comprehensive screening of the English and Japanese literature from three databases published over two decades yielded 1518 reports. These studies were meticulously screened by at least two independent reviewers, focusing on the use of post-acute iNO for PH associated with BPD (BPD-PH) in preterm infants. Using the PCC framework, two distinct groups of reports were identified: one where iNO was utilized prophylactically to prevent development of BPD later, and another where iNO was used as a rescue therapy for preterm infants with BPD-PH. Additionally, miscellaneous reports that did not completely fit within the PCC framework, but still provided valuable insights into post-acute iNO use were also categorized.

Studies investigating prophylactic iNO use for BPD

In this subset of studies, patients were enrolled according to predefined protocols, with iNO administered as planned in terms of duration and dosage. While RCTs allowed for quantitative assessment, gathering clinical information on iNO use and associated complications or adverse events in preterm infants with BPD-PH posed challenges. One RCT published by Ballard et al. in 2006[8] demonstrated the effectiveness of post-acute iNO in promoting survival without BPD, while two other studies did not show significant efficacy.[9, 11] Importantly, large prospective studies reported no adverse events with consistent iNO use.

Studies investigating rescue iNO use for PH

The seven reports in this category constituted the focal point of our review. These studies were retrospective in nature, primarily due to ethical constraints in conducting RCTs in patients with severe clinical courses, necessitating rescue treatment with iNO, especially given the lack of effective alternative therapies.

Among these studies, only a few have clearly described the indications for post-acute iNO use,[12, 14] with only four reports utilizing echocardiography as a criterion for diagnosis of PH.[12, 13, 14, 22] However, the use of echocardiography as the gold standard for diagnosing PH varies among countries due to differences in available resources at the bedside.[7, 26] Nevertheless, to enhance the reliability of accumulated studies, quantitative evaluation using echocardiography is imperative, and should be incorporated into the diagnostic criteria for BPD-PH developed in the post-acute phase.

Employing large-scale multicenter studies or national data analyses, as demonstrated by Nakanishi et al.,[4] may help to overcome the challenges posed by the rarity of the study population and facilitate the acquisition of high-quality data.

Other studies

In addition to studies focusing on rescue iNO use for PH, we obtained valuable insights into clinical settings regarding the use of echocardiography as a diagnostic criterion for PH in the post-acute phase, information on the parameters used in the diagnostic procedure, and the practical utilization of iNO. Furthermore, we identified respiratory severity scores and OSI as potential surrogate parameters for assessing dyspnea.

Considering the rare reporting of complications and comorbidities associated with iNO use, the implementation of post-acute iNO appears to be safe.

Gaps

This scoping review underscores that the utilization of iNO to treat PH in the post-acute phase primarily occurs for rescue purposes. However, reports focusing on rescue purposes were predominantly retrospective, potentially biasing the inclusion of severe cases that led to adverse outcomes following iNO therapy. Additionally, due to the severity of oxygen desaturation in BPD-PH or HRF stemming from various causes, iNO may be initiated prior to a detailed evaluation of the PH status. Alternatively, although neonatologists in Japan implement bedside diagnostic echocardiography prior to administering iNO, this protocol may not be universally adhered to in other developed countries due to logistical issues, even though it is critical for PH diagnosis. Moreover, the clinical settings were not explicitly identified in this review due to insufficient data collection in each report. Another critical issue is the inter-rater variability associated with echocardiography, which needs to be addressed before its widespread adoption as a standard test. Thus, to promote the use of echocardiographic evaluation for PH before iNO administration, a simple and robust parameter must be identified.

Strengths and limitations

To our knowledge, this is the first scoping review to explore the use of iNOs in post-acute settings. However, despite including some reports that did not fully align with our prespecified study concept, the information gathered on the diagnosis of PH was insufficient, leading to unsatisfactory results. The severity of PH associated with BPD

alongside the heterogeneity within the population, such as gestational age or the timing of iNO introduction, even in large-scale studies, further complicates efforts to enhance the quality of evidence regarding post-acute iNO administration. The failure to select patients with PH using echocardiography may be a key reason why the efficacy of post-acute iNO administration has not been convincingly demonstrated, which is a critical issue, given that iNO is a selective vasodilator.

Furthermore, ethical challenges hinder patient recruitment for RCTs examining the efficacy of post-acute iNO administration in patients with BPD-PH. Additionally, collecting comprehensive data, including diagnostic criteria for PH before iNO introduction in the post-acute phase, poses significant challenges in retrospective studies, especially when conducted on a large scale. To address these challenges, it is crucial to conduct prospectively registered cohort studies at the national level or report valuable information from large-scale single-center or multicenter studies. Notably, the low incidence of adverse events or complications associated with iNO use allows for a positive view regarding the introduction of post-acute iNO in preterm infants.

CONCLUSION

This scoping review sheds light on the clinical settings and current utilization of post-acute iNO therapy. Our results showed that the available evidence is insufficient to firmly support the use of post-acute iNO in treating infants with PH associated with BPD. Prospective studies with high-quality evidence are essential to address this knowledge gap. Additionally, given the severity and rarity of this disease, detailed

retrospective studies are also warranted. We believe that accumulating evidence regarding the efficacy and safety of post-acute iNO in preterm infants will pave the way for its appropriate utilization as a promising gaseous agent in this population.

ACKNOWLEDGMENTS

We wish to express our sincere gratitude to Ms. Kuniko Sato, a librarian at St. Luke's International University, for her invaluable assistance in establishing the search strategy.

CONFLICT OF INTEREST

None declared.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. However, this study was supported by the Japan Society for Neonatal Health and Development. The supporting society had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

AUTHOR CONTRIBUTIONS

SK and HN conceptualized this study. All authors contributed to the scope and design of this review. DS and EO developed the search strategy through consultation with the medical librarian at St. Luke's International University, KS. SK, YM, MH, TN, and SI performed the screening, data charting, and data synthesis. SK prepared the first draft, and all other authors provided substantial input for the development of the final version. DS and HN provided feedback on the methodology. All authors have read and revised the draft, and have approved the final version of the manuscript.

DATA SHARING STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

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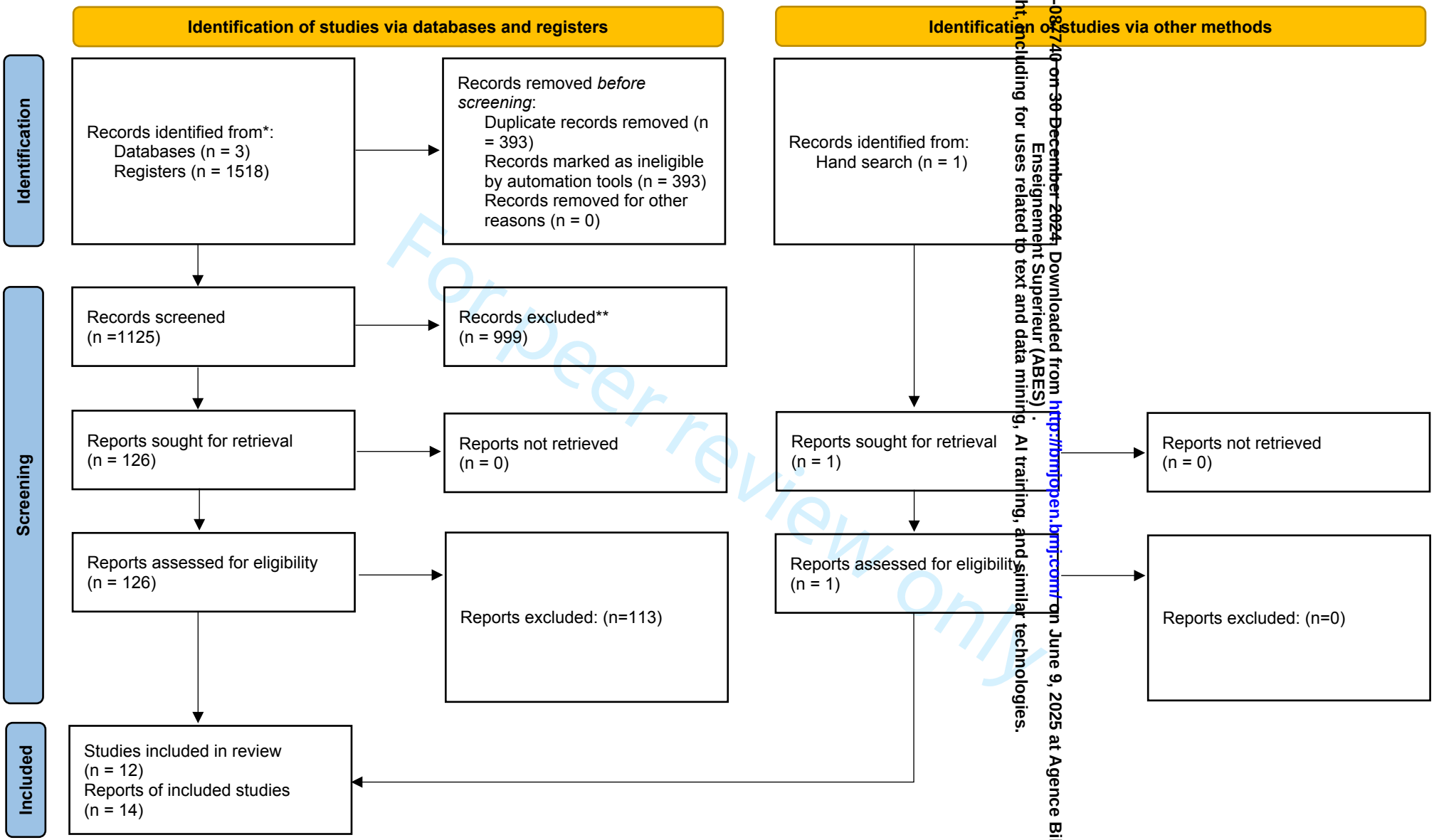
FIGURE LEGEND

Figure 1: Flow diagram showing the study selection process.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Supplementary Figure. Search strategy of the scoping review in Pubmed.

Search number	Query	Sort By	Filters	Search Details	Results
7	#4 and #5 and #6	Most Recent		("infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "pre term*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]) AND ("administration, inhalation"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "iNO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]) AND ("iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract]) AND ("english"[Language] OR "japanese"[Language]) AND 2022/12/01:2023/08/31[Date - Publication]	21
6	("2022/12/01"[Date - Publication] : "2023/08/31"[Date - Publication])	Most Recent		2022/12/01:2023/08/31[Date - Publication]	1,381,989
5	("english"[Language]) OR ("japanese"[Language])	Most Recent		"english"[Language] OR "japanese"[Language]	32,374,912
4	#1 and #2 and #3	Most Recent		("infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "pre term*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]) AND ("administration, inhalation"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "iNO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]) AND ("iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract])	715
3	iNO[tiab] OR "Nitrogen Monoxide"[tiab:~2] OR "Nitric Oxide"[mh] OR "nitric oxide"[tiab:~2] OR "nitric oxides"[tiab:~2] OR "no-inhalation"[tiab]	Most Recent		"iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract]	188,676
2	"Administration, Inhalation"[mh] OR "Administration, Intranasal"[mh] OR "Aerosols"[mh] OR Aerosol*[tiab] OR Atomizer*[tiab] OR Inhala*[tiab] OR inhale*[tiab] OR iNO[tiab] OR nasal[tiab] OR Nebulizer*[tiab] OR "Nebulizers and Vaporizers"[mh] OR "Respiratory Tract Absorption"[mh] OR Vaporizer*[tiab] OR "no-inhalation"[tiab]	Most Recent		"administration, inhalation"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "iNO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]	336,347
1	"Infant, Low Birth Weight"[mh] OR "Infant, Premature"[mh] OR "Infant, Premature, Diseases"[mh] OR LBW[tiab] OR low birth weight*[tiab] OR low birthweight*[tiab] OR "neonatal underweight"[tiab:~3] OR "neonatal under weight"[tiab:~3] OR Prematur*[tiab] OR Preterm*[tiab] OR pre-matur*[tiab] OR Pre-term*[tiab] OR "Premature Birth"[mh] OR VLBW[tiab]	Most Recent		"infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "pre term*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]	312,860

BMJ Open

Scoping review of initiation criteria for inhaled nitric oxide in preterm infants (born <34 weeks) after 7 days of age

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-087740.R1
Article Type:	Original research
Date Submitted by the Author:	12-Oct-2024
Complete List of Authors:	Kato, Shin; Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Department of Pediatrics Minamitani, Yohei; Saitama Medical Center, Department of Pediatrics Hosokawa, Miku; Japanese Red Cross Medical Center, Department of Neonatology Nakashima, Toshinori; National Hospital Organization Kokura Medical Center, Department of Pediatrics Iwatani, Sota; Hyogo Prefectural Kobe Children's Hospital, Department of Neonatology Hirata, Katsuya; Osaka Women's and Children's Hospital Oda, Arata; Nagano Children's Hospital, Division of Neonatology Hanita, Takushi; Tohoku University Hospital, Center for Perinatal and Neonatal Medicine Miyata, Masafumi; Fujita Health University, Department of Pediatrics Namba, Fumihiko; Saitama Medical Center, Department of Pediatrics Ochiai, Masayuki; Kyushu University, Research Center for Environmental and Developmental Medical Sciences Nakao, Atsushi; Japanese Red Cross Medical Center, Department of Neonatology Yoshimoto, Seiji; Hyogo Prefectural Kobe Children's Hospital, Department of Neonatology Suzuki, Daichi; Kanagawa Institute of Technology, Department of Nursing, Faculty of Health & Medical Sciences Ota, Erika; St. Luke's International University, Global School of Nursing Science, Global Health Nursing Nakanishi, Hidehiko; Kitasato University School of Medicine, Department of Pediatrics
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	NEONATOLOGY, PAEDIATRICS, Pulmonary Disease < Lung Diseases

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Scoping review of initiation criteria for inhaled nitric oxide in preterm infants (born <34 weeks) after 7 days of age

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ABSTRACT

Objectives: Inhaled nitric oxide (iNO) is a known treatment for pulmonary hypertension (PH) associated with bronchopulmonary dysplasia in preterm infants after 7 days of age (post-acute phase). However, a consensus regarding the optimal criteria for initiating iNO therapy in this population in the post-acute phase is currently lacking. This study therefore aimed to identify the criteria for initiating iNO therapy, alongside the associated clinical and echocardiographic findings, in this population.

Design: We performed a scoping review using the population–concept–context framework following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.

Data sources: The PubMed, Embase, and the Japanese database "Ichushi" were systematically searched for relevant articles published between January 2003 and August 2023.

Eligibility criteria: This study included randomized controlled trials, prospective and retrospective cohort studies, case-control studies, and case series on iNO therapy in the post-acute phase for preterm infants born before 34 gestational weeks, written in English or Japanese.

Data extraction and synthesis: Data screening, extraction, and charting were performed independently, with the characteristics and findings of the included studies subsequently summarized.

Results: We included 10 reports that analyzed the data from 10 separate studies. The use of iNO therapy was categorized as prophylactic and rescue purpose. While randomized controlled trials and retrospective analyses indicated the safety of iNO during the post-acute

phase, the latter highlighted poor prognoses associated with severe cases requiring rescue iNO therapy. Additionally, although echocardiography is currently the primary diagnostic tool for identifying PH in preterm infants, standardized diagnostic criteria are lacking. Further, reports of complications and side effects associated with iNO are rare.

Conclusion: Our exploration of the initiation criteria for iNO revealed that definitive guidelines have not been established. Nonetheless, iNO administration during the post-acute phase appeared to be safe and devoid of complications.

Trial registration number: UMIN000051498.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.
- The protocol has been published to ensure transparency.
- We searched the Japanese database "Ichushi,'' which has documented a long history of active resuscitation of the most vulnerable preterm newborns.
- The review did not include a quality assessment of the included studies.

INTRODUCTION

Nitric oxide (NO) is a gaseous agent with a targeted effect on pulmonary hypertension (PH), significantly improving outcomes in newborns.[1, 2] In the United States, medical insurance limitations restrict the use of NO before 34 weeks of postmenstrual age. However, experience with inhaled NO (iNO) treatment has accumulated globally, with reports detailing its effect on both short- and long-term prognoses in premature newborns.[3, 4, 5] Bronchopulmonary dysplasia (BPD) significantly impacts pulmonary function and neurodevelopmental outcomes in premature newborns. Moderate-to-severe BPD is recognized as one of the key causes of hypoxic respiratory failure (HRF) or PH in newborns, particularly in the post-acute phase, which can be potentially fatal.[6, 7]

Notably, the efficacy of iNO during the post-acute phase has been documented for both BPD prevention and rescue from HRF or PH.[8, 9, 10] However, its effectiveness remains suboptimal. For example, iNO is not covered by medical insurance when initiated after the first week of life in Japan. Hence, it is imperative to establish evidence supporting its efficacy and broaden its indications to include the post-acute phase.

Despite the increasing off-label use of iNO, the criteria for its initiation vary across studies. Neonatologists have utilized diverse parameters to diagnose hypoxia, including oxygen saturation, arterial oxygen partial pressure, and the oxygenation index.[11, 12, 13] Similarly, various echocardiographic findings are used to diagnose PH.[7, 14] Echocardiography is considered the gold standard for PH diagnosis in newborns; however, logistical challenges may hinder its implementation prior to the initiation of iNO treatment in certain countries. Indeed, iNO is sometimes employed for clinical HRF or PH in the absence of any definitive echocardiographic findings, partly because of the aforementioned reasons. We believe that

the current perceived inadequacy of post-acute iNO therapy may be partly due to the enrollment of heterogeneous populations without a robust diagnosis of PH in prior studies investigating iNO efficacy.[15] In addition, while the mechanism of action of iNO renders it suitable for PH treatment, the optimal initiation criteria, particularly among premature infants in the post-acute phase, remain unclear.

Presently, there is a dearth of comprehensive information regarding the actual usage and initiation criteria for post-acute iNO in Japan and other nations. This review, therefore, aimed to provide a comprehensive overview of existing evidence on the administration of iNO after 7 days of life. It covers initiation criteria as well as dosage, duration, discontinuation criteria, concomitant use of other drugs, and adverse effects.

METHODS AND ANALYSIS

Protocol and registration

The protocol of this scoping review was registered at UMIN-CTR (registration number: UMIN000051498), and was subsequently published.[16] This review was conducted in compliance with the published protocol.

Eligibility criteria

This scoping review followed the Population-Concept-Context (PCC) framework outlined by the Joanna Briggs Institute (Table 1, https://doi.org/10.46658/JBIMES-20-12). Articles meeting the following eligibility criteria were included: (1) articles enrolling preterm infants born at <34 weeks of gestation and aged >7 days; (2) provision of clinical information on iNO usage; (3) publication between January 2003 and August 2023; (4) conducted in developed countries; (5) written in English or Japanese; and (6) encompassing study designs such as

randomized controlled trials (RCTs), prospective and retrospective cohort studies, case-control studies, and case series. The exclusion criteria were as follows: (1) participants with congenital malformation syndrome or chromosomal abnormalities; (2) animal and in vitro studies; and (3) conference abstracts, trial registrations, and protocol publications.

Table 1. PCC framework of this scoping review

Population	Preterm infants born at <34 weeks of gestation and treated with iNO after 7 days of age
Concept	Aim to identify the initiation criteria of iNO, postnatal day of the iNO initiation, dosage of iNO (ppm), duration of iNO therapy, discontinuation criteria of iNO therapy, concomitant use of other drugs, and adverse effects
Context	Published between January 2003 and August 2023 Conducted in developed countries Published in English or Japanese Randomized controlled trial, cohort study, case-control study, and case series Excluding congenital malformation syndrome and a chromosomal abnormality

PCC, Population-Concept-Context; iNO, inhaled nitric oxide

Information sources

We conducted searches across PubMed and Embase, as well as the Japanese electronic bibliographic database "Ichushi." These searches were carried out by an accomplished librarian, supplemented by manual searches conducted by the authors. Given the paradigm shift in BPD to "new BPD" highlighted by Jobe in 1999,[17] alongside the advent of iNO in the clinical neonatology domain around 2000, we limited our search to studies published within the most recent two decades, spanning from January 2003 to August 2023. The search strategies are detailed in the Supplemental Appendix.

Selection of sources of evidence

Our scoping review approach adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist.[18] The search results were deduplicated using EndNote 20, and imported into Rayyan, a web application,[19] to screen eligible studies. The authors (YM, MH, TN, and SI) independently evaluated the titles and abstracts of the identified studies using the PCC framework to ascertain potential eligibility based on the inclusion criteria. Subsequently, a thorough full-text review of potentially eligible studies was performed. Any discrepancies regarding study eligibility were resolved through consensus discussion among the authors or adjudicated by another author's (SK) assessment. The study selection process is illustrated in the PRISMA flow diagram in Figure 1.

Data charting and synthesis of results

The characteristics of the included studies, including the study design, settings, populations, information regarding the provision of iNO therapy, efficacy of iNO therapy, complications, and other relevant findings, were systematically summarized in a pre-designed Excel form (Tables 3 and 4).

Critical appraisal of individual sources of evidence

Given the overarching objective of this scoping review to map existing evidence, an assessment of the risk of bias within the included studies was not undertaken.

Patient and public involvement

This study did not involve patients or members of the public, as only existing articles were analyzed. However, neonatologists participated in the review process and discussed the results.

RESULTS

Selection of sources of evidence

A literature search was conducted on February 1, 2024, yielding 1518 records. Following deduplication, 393 duplicate records were removed. Subsequently, the remaining 1125 records underwent title and abstract screening, resulting in the exclusion of 999 records that did not meet the inclusion criteria. A full-text review of the remaining potentially eligible studies was subsequently performed, leading to the exclusion of an additional 107 citations. Notably, one relevant Japanese study published in 2012 was identified through a manual literature search and included in the review. Ultimately, 18 original records were included in this study.

Characteristics and results of sources of evidence

Studies investigating prophylactic iNO use for BPD

Three RCTs investigated the use of iNO administration to prevent the development of BPD.[8, 9, 11] All of these studies were multicenter and involved a relatively large number of patients, ranging from 451 to 582. The findings of these included studies are summarized in Table 2.

Table 2. Summary of the findings of the included studies

	Author Year	Study design	Country	Setting	Population	Intervention or Concept	Study findings
Studies investigating prophylactic iNO use for BPD							
1	Ballard et al. 2006[8]	RCT	USA	Multicenter (21 centers)	GA; ≤32 weeks BW; 500–1250 g on MV Treatment; 7 and 21 days of age (n=582).	iNO: n=294 N_2: n=288	Survival without BPD; 43.9% in NO and 36.8 % in placebo (RB: 1.23, 95% CI: 1.01–1.51, P=0.042) iNO group discharged sooner (P=0.04), shorter supplemental oxygen use (P=0.006). There was no short-term safety concerns and no difference in the complications of prematurity.
2	Ballard et al. 2016[11]	RCT	USA	Multicenter (25 centers)	GA; ≤28 weeks on MV Treatment; 7 and 14 days of age (n=511)	iNO+surfactant: n=252 iNO only (control): n=259	Survival without BPD; 36 weeks, 31.3% vs. 31.7%, RB: 0.98, (95% CI: 0.75–1.28 P=0.89); 40 weeks, 58.7% vs. 54.1%, RB: 1.08, (95% CI: 0.92–1.27 P=0.33). There was no difference in serious adverse events, comorbidities of prematurity, and the severity of lung disease at 36 weeks.
3	Hasan et al. 2017[9]	RCT	Canada	Multicenter (33 centers)	GA; <30 weeks Treatment; respiratory support on 5–14 days of age (n=451)	iNO: at 7 and 14 days of age iNO: n=175 N_2: n=175	Survival without BPD was not improved at 36 weeks. Respiratory and neurodevelopmental outcomes were not different at 18–24 months of postmenstrual age. There was no difference in the common complications of prematurity.
Studies investigating rescue iNO use for PH							
4	Truog et al. 2014[10]	Retrospective cohort	USA	Multicenter (13 centers)	GA; <29 weeks, BW; 400–1000 g (n=187)	iNO started at ≥7 days of age	iNO administration between days 7 and 14 was associated with an increased risk of BPD or death (OR: 2.24, 95%CI: 1.23–4.07). No information regarding complications or adverse events of iNO use was reported.
5	Hsiao et al. 2019[20]	Retrospective cohort	Taiwan	Single tertiary center	GA; 30.5 (26.0–36.5) weeks, BW; 1305 (788.5–2532) g, (n = 27)	Off-label use of iNO as "final rescue" for refractory hypoxemia (not for PPHN)	Common causes of off-label iNO use included BPD (19/27, 70.4%) and secondary PH (14/27, 51.9%) The Off-label iNO use group demonstrated the poorest response and the highest in-hospital mortality (P <0.001).

6	Nakanishi et al. 2023[4]	Retrospective cohort	Japan	Multicenter (NRNJ database)	GA; <28 weeks (n=462)	Post-acute iNO (iNO use in the late phase of hospitalization without PPHN)	Post-acute iNO use increased in extremely preterm infants with more severe disease and complications. Post-acute iNO was not associated with long-term neurodevelopmental outcomes at 3 years of age.
7	Oka et al. 2023[13]	Retrospective cohort	Japan	Single tertiary center	GA; <28 weeks, BW; 620 (482–814) g, (n=30)	iNO after 96 h of age (not for PPHN)	iNO therapy-related adverse events were not reported. There was no difference in in-hospital outcomes between responders and non-responders. Methemoglobinemia (MetHb >5%) did not occur in any participant. Early iNO was associated with treatment response (OR: 0.89, 95% CI: 0.7970–0.995, P=0.04)
8	Fraga et al. 2023[14]	Prospective cohort	USA	Single tertiary center	GA; 25 weeks (24–27), (n=37)	iNO used at cGA ≥36 weeks, 40 weeks (37–43) at study entry (n=37)	Thirty (81%) patients had echocardiographic evidence of PAH before iNO, and 19 (56%) after 48 h of iNO (P=0.04). FiO_2 requirements were significantly different between time points before initiation of iNO and after 48–168 h (P=0.05).
9	Nakao et al. 2012[21]	Retrospective cohort	Japan	Single tertiary center	GA; 24 weeks (22–28) BW 507.5 g (320–710 g) (n=12)	iNO used at ≥ 7 days	Indication; HRF with PH (n=10), CLD with PH (n=3) Outcome; Death (n=8) No complications were reported
10	Iwatani et al. 2022[22]	Retrospective cohort	Japan	Multicenter (10 centers)	GA; <28 weeks (23–27), BW; 417–1070 g (n=12)	iNO used at ≥ 7 days	Background; Histological CAM (n=9), SGA (<-3 SD) (n=2) Indication; CLD with PH (n=7), HRF with PH (n=5) Outcome; Death (n=8), HOT (n=3), tracheostomy (n=1)

iNO, inhaled nitric oxide; GA, gestational age; BW, birth weight; RB, relative benefit; CI, confidence interval; OR, odds ratio; BPD, bronchopulmonary dysplasia; RCT, randomized controlled trial; PH, pulmonary hypertension; HRF, hypoxic respiratory failure; LVEF, left ventricular ejection fraction; NRNJ, Neonatal Research Network of Japan; IQR, interquartile range; PAH; pulmonary artery hypertention, CLD; chronic lung disease, CAM; chorioamnionitis, SGA; small for gestational age, HOT; home oxygen therapy, LVEF; left ventricle ejection fraction, PPHN; persistent pulmonary hypertention of the newborn, MV; mechanical ventilation

All studies included in the analysis investigated survival without BPD as the primary outcome. Among them, only one study showed the efficacy of iNO within the treated group (relative benefit: 1.23, 95% confidence interval: 1.01–1.51, P=0.042),[8] while the remaining studies did not demonstrate improvement.[9, 11] None of the studies reported an increase in short-term outcomes or prematurity-associated comorbidities. Additionally, it is worth mentioning that although the study by Hasan enrolled newborns between 5 and 14 days of age, it did not specify when iNO therapy was initiated. Nevertheless, we included this study as it yielded significant findings, demonstrating no difference in respiratory or neurodevelopmental outcomes at 18 to 24 months postmenstrual age.[20]

Studies investigating rescue iNO use for HRF and PH

Seven studies focused on the use of iNO for rescue purposes. These studies comprised two database analyses,[4, 10] four retrospective cohort studies conducted in single tertiary centers,[13, 14, 20, 21] and one multicenter retrospective cohort study.[22] Additionally, we included two retrospective reports in Japanese, and summarized their results by extracting patient information that matched the study concept provided by the authors.[21, 22] The number of participants ranged from 12 to 462. A summary of these studies is presented in Table 2. Among these studies, four reported worse respiratory outcomes, and four reported death before discharge. Oka et al.[13] noted a positive response to post-acute iNO, defined as a >20% reduction in the oxygen saturation index (OSI), when introduced earlier. They also found no difference in the incidence of in-hospital outcomes between responders and non-responders. Despite finding that two newborns received iNO treatment on day 6 of life and another on day 5, we included this study as the majority of the included newborns matched the inclusion criteria. Nakanishi et al.[4] reported in their retrospective cohort study using the

Neonatal Research Network of Japan (NRNJ) database that there was no increase in developmental outcome at 3 years of age following post-acute iNO treatment. Fraga et al.[14] emphasized the importance of echocardiographic assessment of PH in infants with severe BPD before initiating iNO.

Synthesis of results

Initiation criteria for post-acute iNO

While the diagnostic criteria for PH are often poorly described in the literature, they are essential for the effective and safe administration of iNO in the post-acute phase. Among three studies focusing on iNO prophylaxis for BPD, none reported the diagnostic criteria for PH due to the nature of the studies.[8, 9, 11] However, in five studies examining the use of echocardiography to diagnose PH before iNO initiation, various criteria were reported.[12, 13, 14, 20, 22] Specifically, four studies identified ventricular septal wall flattening or bowing in the end-systole or pulmonary artery (PA) pressure elevation as indicators of PH.[12, 13, 14, 22] Fraga et al. further provided additional detailed echocardiographic findings for PH diagnosis, such as right-to-left shunting at the patent foramen ovale (PFO) or patent ductus arteriosus (PDA) level and the tricuspid peak velocity (TPV):right ventricular ejection time (RVET) ratio, as markers for PA pressure (PAP) elevation.[14] Accurate diagnosis of nitric-responsive PH, excluding conditions including left ventricular dysfunction, is critical. Echocardiography performed by a neonatologist before iNO initiation should be considered a crucial step.

To measure the severity of respiratory compromise, various measures have been utilized. Three studies employed the respiratory severity index (mean airway pressure [MAP] × fraction of inspired oxygen [FiO_2]),[8, 11, 12] one utilized the OSI,[13] and two employed the oxygenation index.[12, 21] In out-of-concept studies, Hussein et al. reported the use of

echocardiography for PH diagnosis and noted echocardiographic findings, including flattened ventricular septum, tricuspid regurgitation (TR), and right-to-left shunt at the PFO/PDA level.[12] They also reported a 60% reduction in iNO use following the implementation of a weaning protocol.

A summary of these findings is presented in Table 3.

Table 3. Initiation criteria for iNO in all of the included studies

	Author	Initiation criteria for iNO			
		PH diagnosis	Echocardiographic findings	Surrogate marker of disease severity	Others
1	Ballard et al. 2006	N/A	N/A	MAP×FiO_2	N/A
2	Ballard et al. 2016	N/A	N/A	MAP×FiO_2	N/A
3	Hasan et al. 2017	N/A	N/A	N/A	N/A
4	Truog et al. 2014	N/A	N/A	N/A	N/A
5	Hsiao et al. 2019	Echocardiography	Details were not available	N/A	N/A
6	Nakanishi et al. 2023	N/A	N/A	N/A	N/A
7	Oka et al. 2023	Echocardiography (24%)	TR (PA>40 mmHg) D-shaped LV	OSI = MAP×FIO_2×100 /SpO_2	N/A
8	Fraga et al. 2023	Echocardiography	RV pressure >½ sSBP estimated from TRJV. Bidirectional or right-to-left shunting	N/A	N/A

			through a PDA. Septal flattening or bowing at end-systole. TPV:RVET ratio, 0.2–0.3, moderately elevated PAP; ≤0.2, significantly elevated PAP.		
9	Nakao et al. 2012	N/A	N/A	Oxygenation index	N/A
10	Iwatani et al. 2022	Cyanosis echocardiography	TR D-shaped LV	N/A	N/A

OSI, oxygen saturation index; pulmonary artery; TPV, tricuspid peak velocity; RVET, right ventricular ejection time; PAP, pulmonary artery pressure; MAP, mean airway pressure; FiO_2, fraction of inspired oxygen; TR, tricuspid regurgitation; iNO, inhaled nitric oxide; RV, right ventricle; LV, left ventricle; sSBP, systolic systemic blood pressure; PaO_2, partial pressure of oxygen; SpO_2, peripheral oxygen saturation; TRJV, tricuspid regurgitant jet velocity; HRF, hypoxic respiratory failure

Details of post-acute iNO administration

The starting dose of iNO ranged from 3–20 ppm, with four studies starting at 20 ppm[8, 9, 11, 20], and one study reporting a maximum dose of 80 ppm.[20] The duration of iNO administration varied widely, ranging from 2 to 314 days. The extended duration of iNO treatment may be attributed to its utilization as a rescue therapy in post-acute cases. Notably, three RCTs included a 24-day pre-protocol dosing period.[8, 9, 11] Regarding adjunctive medications, reports involving the use of surfactants,[11, 13, 20] inotropes,[12, 20] corticosteroids[13], bronchodilators[14], and diuretics[14] were included. RCTs did not report significant differences in adverse events or increases in complications related to preterm

birth,[8, 9, 11] which aligns with the findings of retrospective studies.[4, 12, 13, 21, 22] However, one case of pulmonary edema was reported after 48–168 h of iNO administration, without evidence of left ventricle dysfunction based on echocardiography.[14] The criteria for discontinuation are not well-described. Regarding RCTs [8, 9, 11], they were designated as protocol treatment. However, for rescue treatment, they probably could not be stopped [13, 14, 20, 21, 22]. Additionally, for retrospective studies [4,10], it may not be possible to retrieve these data. Hussain implemented a weaning protocol at their institution and successfully reduced the total iNO hours from 149 h to 59 h; however, the study was excluded from our review because it did not align with the study concept [12].

A summary of these data is presented in Table 4.

Table 4. Summary of the details of post-acute iNO administration in preterm infants in the included studies

	Author Year	Postnatal day of iNO initiation	Dosage of iNO (ppm)	Duration of iNO	Other drugs	Discontinuation criteria	Adverse effects
1	Ballard et al. 2006	7–21 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	N/A	Specified by the protocol	No difference in the complications of prematurity No methemoglobinemia
2	Ballard et al. 2016	7–14 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	Surfactant	Specified by the protocol	No difference in severe adverse events and complications of prematurity
3	Hasan et al. 2017	7–14 days	Start with 20 ppm Decreased to 10 ppm in 72–96 h Then 5 ppm on day 10 or 11 Remain at 5 ppm until completion of therapy for 24 days	Minimum 24 days	N/A	Specified by the protocol	No differences in common complications of prematurity No elevation in NO_2 or methemoglobin level
4	Truog et al. 2014	7–28 days: (n=140 or 2.9%) >28 days: (n=47 or 0.96%)	N/A	N/A	N/A	N/A	N/A
5	Hsiao et al. 2019	> 7 days	Start with 20 ppm (rarely 10 ppm) Increased to 40 ppm without clinical response (max 80 ppm)	N/A	Surfactant 1/27 (3.7%) Dopamine 10/27 (37.0%) Dobutamine 6/27 (22.2%) Epinephrine 3/27 (11.1%)	N/A	N/A

					Milrinone 6/27 (22.2%)		
6	Nakanishi et al. 2023	N/A (post-acute iNO; defined as iNO administration in the late phase of hospitalization)	N/A	26 days [14–70 days]	N/A	N/A	N/A
7	Oka et al. 2023	19 (11–26) days	Starting dose: 10 ppm	20.5 (8–32.5) days	Surfactant corticosteroid	N/A	No complications No methemoglobinemia
8	Fraga et al. 2023	40 weeks (37–43)	20 ppm	N/A	Bronchodilators; n=16 (43%) Diuretics; Furosemide: n=15 (40%), Chlorothiazide: n=16 (43%)	N/A	Pulmonary edema; n=1
9	Nakao et al. 2012	>7 days (214–2880 h)	Starting dose: 3–20 ppm Highest dose: 5–40 ppm	Median 130 h (22–1330 h)	N/A	N/A	No complications
10	Iwatani et al. 2022	39 (12–142) day	N/A	2–36 days	N/A	N/A	No methemoglobinemia No jaundice

iNO, inhaled nitric oxide

DISCUSSION

Summary of evidence

In this scoping review, a comprehensive screening of the English and Japanese literature from three databases published over two decades yielded 1518 reports. These studies were meticulously screened by at least two independent reviewers, focusing on the use of post-acute iNO for PH associated with BPD (BPD-PH) in preterm infants. Using the PCC framework, two distinct groups of reports were identified: one where iNO was utilized prophylactically to prevent development of BPD later, and another where iNO was used as a rescue therapy for preterm infants with BPD-PH.

Studies investigating prophylactic iNO use for BPD

In this subset of studies, patients were enrolled according to predefined protocols, with iNO administered as planned in terms of duration and dosage. While RCTs allowed for quantitative assessment, gathering clinical information on iNO use and associated complications or adverse events in preterm infants with BPD-PH posed challenges. One RCT published by Ballard et al. in 2006[8] demonstrated the effectiveness of post-acute iNO in promoting survival without BPD, while two other studies did not show significant efficacy.[9, 11] Importantly, large prospective studies reported no adverse events with consistent iNO use.

Studies investigating rescue iNO use for PH

The seven reports in this category constituted the focal point of our review. These studies were retrospective in nature, primarily due to ethical constraints in conducting RCTs in patients with severe clinical courses, necessitating rescue treatment with iNO, especially given the lack of effective alternative therapies.

Among these studies, only a few have clearly described the indications for post-acute iNO use,[12, 14] with only three reports utilizing echocardiography as a criterion for diagnosis of PH.[13, 14, 22] However, the use of echocardiography as the gold standard for diagnosing PH varies among countries due to differences in available resources at the bedside.[7, 23] Nevertheless, to enhance the reliability of accumulated studies, quantitative evaluation using echocardiography is imperative, and should be incorporated into the diagnostic criteria for BPD-PH developed in the post-acute phase.

Employing large-scale multicenter studies or national data analyses, as demonstrated by Nakanishi et al.,[4] may help to overcome the challenges posed by the rarity of the study population and facilitate the acquisition of high-quality data.

Other findings

Among the studies mentioned above, we obtained valuable insights into clinical settings regarding the use of echocardiography as a diagnostic criterion for PH in the post-acute phase, information on the parameters used in the diagnostic procedure, and the practical utilization of iNO. Furthermore, we identified respiratory severity scores and OSI as potential surrogate parameters for assessing dyspnea. Considering the rare reporting of complications and comorbidities associated with iNO use, the implementation of post-acute iNO appears to be safe.

Gaps

This scoping review underscores that the utilization of iNO to treat PH in the post-acute phase primarily occurs for rescue purposes. However, reports focusing on rescue purposes were predominantly retrospective, potentially biasing the inclusion of severe cases that led to adverse outcomes following iNO therapy. Additionally, due to the severity of oxygen desaturation in BPD-PH or HRF stemming from various causes, iNO may be initiated prior to

a detailed evaluation of the PH status. Alternatively, although neonatologists in Japan implement bedside diagnostic echocardiography prior to administering iNO, this protocol may not be universally adhered to in other developed countries due to logistical issues, even though it is critical for PH diagnosis. Moreover, the clinical settings were not explicitly identified in this review due to insufficient data collection in each report. Another critical issue is the inter-rater variability associated with echocardiography, which needs to be addressed before its widespread adoption as a standard test. It is essential to promote the use of comprehensive echocardiographic evaluation for PH before administering iNO. While identifying a simple and robust parameter may help streamline the process, it is crucial to consider a holistic approach that encompasses multiple diagnostic criteria to ensure an accurate and effective diagnosis.

Strengths and limitations

To our knowledge, this is the first scoping review to explore the use of iNOs in post-acute settings. However, despite including some reports that did not fully align with our prespecified study concept, the information gathered on the diagnosis of PH was insufficient, leading to unsatisfactory results. The severity of PH associated with BPD alongside the heterogeneity within the population, such as gestational age or the timing of iNO introduction, even in large-scale studies, further complicates efforts to enhance the quality of evidence regarding post-acute iNO administration. The failure to select patients with PH using echocardiography may be a key reason why the efficacy of post-acute iNO administration has not been convincingly demonstrated, which is a critical issue, given that iNO is a selective vasodilator.

Furthermore, ethical challenges hinder patient recruitment for RCTs examining the efficacy of post-acute iNO administration in patients with BPD-PH. Additionally, collecting

comprehensive data, including diagnostic criteria for PH before iNO introduction in the post-acute phase, poses significant challenges in retrospective studies, especially when conducted on a large scale. To address these challenges, it is crucial to conduct prospectively registered cohort studies at the national level or report valuable information from large-scale single-center or multicenter studies. Notably, the low incidence of adverse events or complications associated with iNO use allows for a positive view regarding the introduction of post-acute iNO in preterm infants.

CONCLUSION

This scoping review sheds light on the clinical settings and current utilization of post-acute iNO therapy. Our results showed that the available evidence is insufficient to firmly support the use of post-acute iNO in treating infants with PH associated with BPD. Prospective studies with high-quality evidence are essential to address this knowledge gap. Additionally, given the severity and rarity of this disease, detailed retrospective studies are also warranted. We believe that accumulating evidence regarding the efficacy and safety of post-acute iNO in preterm infants will pave the way for its appropriate utilization as a promising gaseous agent in this population.

ACKNOWLEDGMENTS

We wish to express our sincere gratitude to Ms. Kuniko Sato, a librarian at St. Luke's International University, for her invaluable assistance in establishing the search strategy.

CONFLICT OF INTEREST

None declared.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. However, this study was supported by the Japan Society for Neonatal Health and Development. The supporting society had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

AUTHOR CONTRIBUTIONS

SK and HN conceptualized this study. All authors (SK, YM, MH, TN, SI, KH, AO, TH, MM, FN, MO, AN, SY, DS, EO, and HN) contributed to the scope and design of this review. DS and EO developed the search strategy through consultation with the medical librarian at St. Luke's International University, KS. SK, YM, MH, TN, and SI performed the screening, data charting, and data synthesis. SK prepared the first draft, and all other authors provided substantial input for the development of the final version. DS and HN provided feedback on the methodology. All authors (SK, YM, MH, TN, SI, KH, AO, TH, MM, FN, MO, AN, SY, DS, EO, and HN) have read and revised the draft, and have approved the final version of the manuscript. SK is responsible for the overall content as guarantor.

DATA SHARING STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

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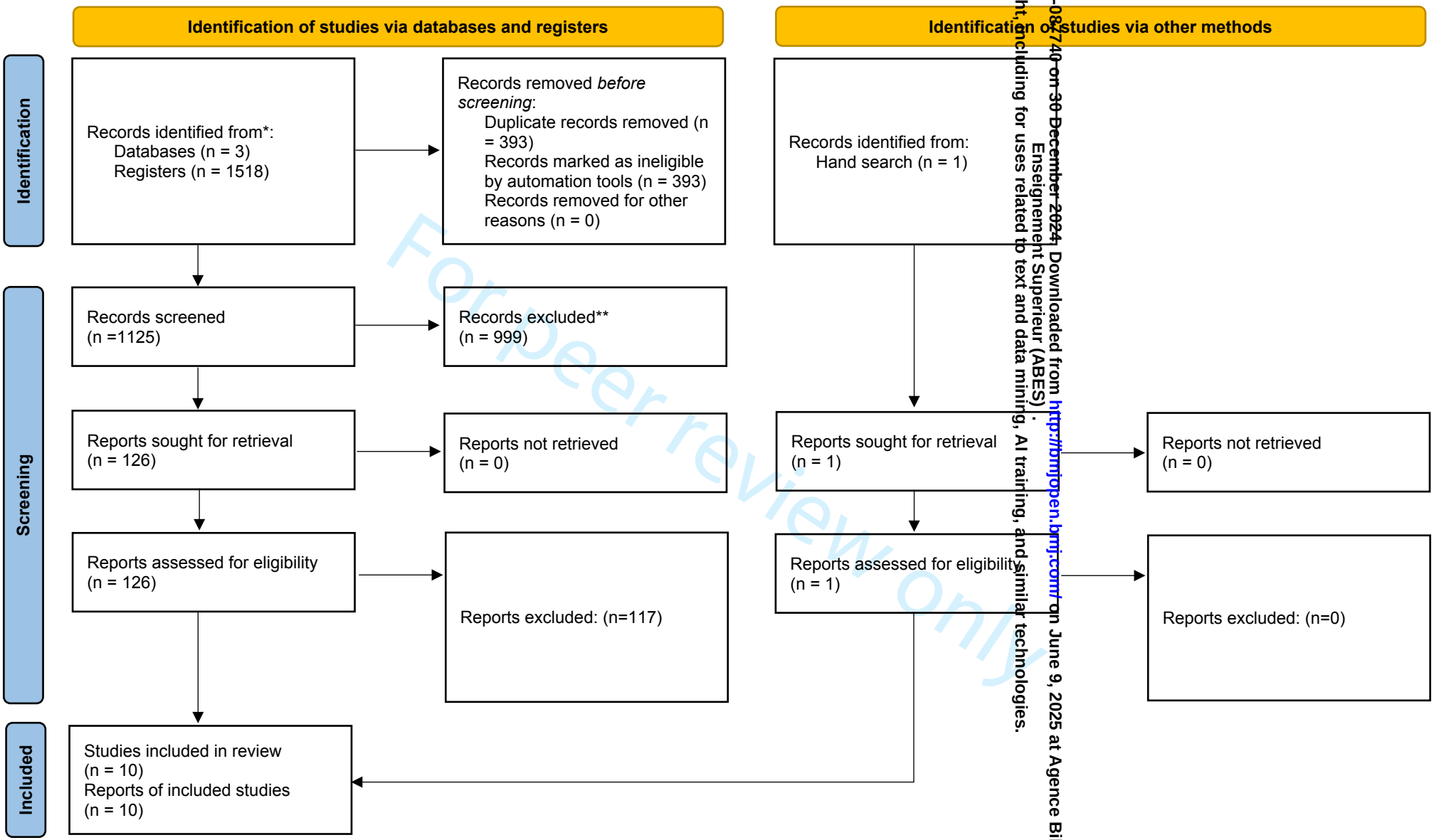
FIGURE LEGEND

Figure 1: Flow diagram showing the study selection process.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Supplementary Figure. Search strategy of the scoping review in Pubmed.

Search number	Query	Sort By	Filters	Search Details	Results
7	#4 and #5 and #6	Most Recent		("infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "pre term*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]) AND ("administration, inhalation"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "iNO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]) AND ("iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract]) AND ("english"[Language] OR "japanese"[Language]) AND 2022/12/01:2023/08/31[Date - Publication]	21
6	("2022/12/01"[Date - Publication] : "2023/08/31"[Date - Publication])	Most Recent		2022/12/01:2023/08/31[Date - Publication]	1,381,989
5	("english"[Language]) OR ("japanese"[Language])	Most Recent		"english"[Language] OR "japanese"[Language]	32,374,912
4	#1 and #2 and #3	Most Recent		("infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "pre term*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]) AND ("administration, inhalation"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "iNO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]) AND ("iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract])	715
3	iNO[tiab] OR "Nitrogen Monoxide"[tiab:~2] OR "Nitric Oxide"[mh] OR "nitric oxide"[tiab:~2] OR "nitric oxides"[tiab:~2] OR "no-inhalation"[tiab]	Most Recent		"iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract]	188,676
2	"Administration, Inhalation"[mh] OR "Administration, Intranasal"[mh] OR "Aerosols"[mh] OR Aerosol*[tiab] OR Atomizer*[tiab] OR Inhala*[tiab] OR inhale*[tiab] OR iNO[tiab] OR nasal[tiab] OR Nebulizer*[tiab] OR "Nebulizers and Vaporizers"[mh] OR "Respiratory Tract Absorption"[mh] OR Vaporizer*[tiab] OR "no-inhalation"[tiab]	Most Recent		"administration, inhalation"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "iNO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]	336,347
1	"Infant, Low Birth Weight"[mh] OR "Infant, Premature"[mh] OR "Infant, Premature, Diseases"[mh] OR LBW[tiab] OR low birth weight*[tiab] OR low birthweight*[tiab] OR "neonatal underweight"[tiab:~3] OR "neonatal under weight"[tiab:~3] OR Prematur*[tiab] OR Preterm*[tiab] OR pre-matur*[tiab] OR Pre-term*[tiab] OR "Premature Birth"[mh] OR VLBW[tiab]	Most Recent		"infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "pre term*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]	312,860

BMJ Open

Scoping review of initiation criteria for inhaled nitric oxide in preterm infants (born <34 weeks) after 7 days of age

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-087740.R2
Article Type:	Original research
Date Submitted by the Author:	17-Nov-2024
Complete List of Authors:	Kato, Shin; Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Department of Pediatrics Minamitani, Yohei; Saitama Medical Center, Department of Pediatrics Hosokawa, Miku; Japanese Red Cross Medical Center, Department of Neonatology Nakashima, Toshinori; National Hospital Organization Kokura Medical Center, Department of Pediatrics Iwatani, Sota; Hyogo Prefectural Kobe Children's Hospital, Department of Neonatology Hirata, Katsuya; Osaka Women's and Children's Hospital Oda, Arata; Nagano Children's Hospital, Division of Neonatology Hanita, Takushi; Tohoku University Hospital, Center for Perinatal and Neonatal Medicine Miyata, Masafumi; Fujita Health University, Department of Pediatrics Namba, Fumihiko; Saitama Medical Center, Department of Pediatrics Ochiai, Masayuki; Kyushu University, Research Center for Environmental and Developmental Medical Sciences Nakao, Atsushi; Japanese Red Cross Medical Center, Department of Neonatology Yoshimoto, Seiji; Hyogo Prefectural Kobe Children's Hospital, Department of Neonatology Suzuki, Daichi; Kanagawa Institute of Technology, Department of Nursing, Faculty of Health & Medical Sciences Ota, Erika; St. Luke's International University, Global School of Nursing Science, Global Health Nursing Nakanishi, Hidehiko; Kitasato University School of Medicine, Department of Pediatrics
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	NEONATOLOGY, PAEDIATRICS, Pulmonary Disease < Lung Diseases

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Scoping review of initiation criteria for inhaled nitric oxide in preterm infants (born <34 weeks) after 7 days of age

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ABSTRACT

Objectives: Inhaled nitric oxide (iNO) is a known treatment for pulmonary hypertension (PH) associated with bronchopulmonary dysplasia in preterm infants after 7 days of age (post-acute phase). However, a consensus regarding the optimal criteria for initiating iNO therapy in this population in the post-acute phase is currently lacking. This study therefore aimed to identify the criteria for initiating iNO therapy, alongside the associated clinical and echocardiographic findings, in this population.

Design: We performed a scoping review using the population–concept–context framework following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.

Data sources: The PubMed, Embase, and the Japanese database "Ichushi" were systematically searched for relevant articles published between January 2003 and August 2023.

Eligibility criteria: This study included randomized controlled trials, prospective and retrospective cohort studies, case-control studies, and case series on iNO therapy in the post-acute phase for preterm infants born before 34 gestational weeks, written in English or Japanese.

Data extraction and synthesis: Data screening, extraction, and charting were performed independently, with the characteristics and findings of the included studies subsequently summarized.

Results: We included 10 reports that analyzed the data from 10 separate studies. The use of iNO therapy was categorized as prophylactic and rescue purpose. While randomized controlled trials and retrospective analyses indicated the safety of iNO during the post-acute

phase, the latter highlighted poor prognoses associated with severe cases requiring rescue iNO therapy. Additionally, although echocardiography is currently the primary diagnostic tool for identifying PH in preterm infants, standardized diagnostic criteria are lacking. Further, reports of complications and side effects associated with iNO are rare.

Conclusion: Our exploration of the initiation criteria for iNO revealed that definitive guidelines have not been established. Nonetheless, iNO administration during the post-acute phase appeared to be safe and devoid of complications.

Trial registration number: UMIN000051498.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.
- The protocol has been published to ensure transparency.
- We searched the Japanese database "Ichushi,'' which has documented a long history of active resuscitation of the most vulnerable preterm newborns.
- The review did not include a quality assessment of the included studies.

INTRODUCTION

Nitric oxide (NO) is a gaseous agent with a targeted effect on pulmonary hypertension (PH), significantly improving outcomes in newborns.[1, 2] In the United States, medical insurance limitations restrict the use of NO before 34 weeks of postmenstrual age. However, experience with inhaled NO (iNO) treatment has accumulated globally, with reports detailing its effect on both short- and long-term prognoses in premature newborns.[3, 4, 5] Bronchopulmonary dysplasia (BPD) significantly impacts pulmonary function and neurodevelopmental outcomes in premature newborns. Moderate-to-severe BPD is recognized as one of the key causes of hypoxic respiratory failure (HRF) or PH in newborns, particularly in the post-acute phase, which can be potentially fatal.[6, 7]

Notably, the efficacy of iNO during the post-acute phase has been documented for both BPD prevention and rescue from HRF or PH.[8, 9, 10] However, its effectiveness remains suboptimal. For example, iNO is not covered by medical insurance when initiated after the first week of life in Japan. Hence, it is imperative to establish evidence supporting its efficacy and broaden its indications to include the post-acute phase.

Despite the increasing off-label use of iNO, the criteria for its initiation vary across studies. Neonatologists have utilized diverse parameters to diagnose hypoxia, including oxygen saturation, arterial oxygen partial pressure, and the oxygenation index.[11, 12, 13] Similarly, various echocardiographic findings are used to diagnose PH.[7, 14] Echocardiography is considered the gold standard for PH diagnosis in newborns; however, logistical challenges may hinder its implementation prior to the initiation of iNO treatment in certain countries. Indeed, iNO is sometimes employed for clinical HRF or PH in the absence of any definitive echocardiographic findings, partly because of the aforementioned reasons. We believe that

the current perceived inadequacy of post-acute iNO therapy may be partly due to the enrollment of heterogeneous populations without a robust diagnosis of PH in prior studies investigating iNO efficacy.[15] In addition, while the mechanism of action of iNO renders it suitable for PH treatment, the optimal initiation criteria, particularly among premature infants in the post-acute phase, remain unclear.

Presently, there is a dearth of comprehensive information regarding the actual usage and initiation criteria for post-acute iNO in Japan and other nations. This review, therefore, aimed to provide a comprehensive overview of existing evidence on the administration of iNO after 7 days of life. It covers initiation criteria as well as dosage, duration, discontinuation criteria, concomitant use of other drugs, and adverse effects.

METHODS AND ANALYSIS

Protocol and registration

The protocol of this scoping review was registered at UMIN-CTR (registration number: UMIN000051498), and was subsequently published.[16] This review was conducted in compliance with the published protocol.

Eligibility criteria

This scoping review followed the Population-Concept-Context (PCC) framework outlined by the Joanna Briggs Institute (Table 1, https://doi.org/10.46658/JBIMES-20-12). We defined the post-acute phase as the late phase of primary hospitalization, i.e. after 7 days of life, based on the definition in previous nationwide surveys by Truog et al.[4] and Nakanishi et al.[6] We employed the 7th day of life as the transition point to exclude premature infants suffering from pulmonary hypertension of the newborn. Articles meeting the following

eligibility criteria were included: (1) articles enrolling preterm infants born at <34 weeks of gestation and aged >7 days; (2) provision of clinical information on iNO usage; (3) publication between January 2003 and August 2023; (4) conducted in developed countries; (5) written in English or Japanese; and (6) encompassing study designs such as randomized controlled trials (RCTs), prospective and retrospective cohort studies, case-control studies, and case series. The exclusion criteria were as follows: (1) participants with congenital malformation syndrome or chromosomal abnormalities; (2) animal and in vitro studies; and (3) conference abstracts, trial registrations, and protocol publications.

Table 1. PCC framework of this scoping review

Population	Preterm infants born at <34 weeks of gestation and treated with iNO after 7 days of age
Concept	Aim to identify the initiation criteria of iNO, postnatal day of the iNO initiation, dosage of iNO (ppm), duration of iNO therapy, discontinuation criteria of iNO therapy, concomitant use of other drugs, and adverse effects
Context	Published between January 2003 and August 2023 Conducted in developed countries Published in English or Japanese Randomized controlled trial, cohort study, case-control study, and case series

Excluding congenital malformation syndrome and a chromosomal abnormality

PCC, Population-Concept-Context; iNO, inhaled nitric oxide

Information sources

We conducted searches across PubMed and Embase, as well as the Japanese electronic bibliographic database "Ichushi." These searches were carried out by an accomplished librarian, supplemented by manual searches conducted by the authors. Given the paradigm shift in BPD to "new BPD" highlighted by Jobe in 1999,[17] alongside the advent of iNO in the clinical neonatology domain around 2000, we limited our search to studies published within the most recent two decades, spanning from January 2003 to August 2023. The search strategies are detailed in the Supplemental Appendix 1.

Selection of sources of evidence

Our scoping review approach adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist. (Supplemental Appendix 2)[18] The search results were deduplicated using EndNote 20, and imported into Rayyan, a web application,[19] to screen eligible studies. The authors (YM, MH, TN, and SI) independently evaluated the titles and abstracts of the identified studies using the PCC framework to ascertain potential eligibility based on the inclusion criteria. Subsequently, a thorough full-text review of potentially eligible studies was performed. Any discrepancies regarding study eligibility were resolved through consensus discussion among the authors or adjudicated by another author's (SK) assessment. The study selection process is illustrated in the PRISMA flow diagram in Figure 1.

Data charting and synthesis of results

The characteristics of the included studies, including the study design, settings, populations, information regarding the provision of iNO therapy, efficacy of iNO therapy, complications, and other relevant findings, were systematically summarized in a pre-designed Excel form (Tables 2 to 4).

Critical appraisal of individual sources of evidence

Given the overarching objective of this scoping review to map existing evidence, an assessment of the risk of bias within the included studies was not undertaken.

Patient and public involvement

This study did not involve patients or members of the public, as only existing articles were analyzed. However, neonatologists participated in the review process and discussed the results.

RESULTS

Selection and characteristics of sources of evidence

A literature search was conducted on February 1, 2024, yielding 1518 records. Following deduplication, 393 duplicate records were removed. Subsequently, the remaining 1125 records underwent title and abstract screening, resulting in the exclusion of 999 records that did not meet the inclusion criteria. A full-text review of the remaining potentially eligible studies was subsequently performed, leading to the exclusion of an additional 117 citations. Notably, one relevant Japanese study published in 2012 was identified through a manual literature search and included in the review. Ultimately, 10 original records were included in this study. The findings of these included studies are summarized in Table 2.

Table 2. Summary of the findings of the included studies

	Author Year	Study design	Country	Setting	Population	Intervention or Concept	Study findings
Studies investigating prophylactic iNO use for BPD							
1	Ballard et al. 2006[8]	RCT	USA	Multicenter (21 centers)	GA; ≤32 weeks BW; 500–1250 g on MV Treatment; 7 and 21 days of age (n=582).	iNO: n=294 N_2: n=288	Survival without BPD; 43.9% in NO and 36.8 % in placebo (RB: 1.2, 95% CI: 1.01–1.51, P=0.042) iNO group discharged sooner (P=0.04), shorter supplemental oxygen use (P=0.006). There were no short-term safety concerns and no difference in the complications of prematurity.
2	Ballard et al. 2016[11]	RCT	USA	Multicenter (25 centers)	GA; ≤28 weeks on MV Treatment; 7 and 14 days of age (n=511)	iNO+surfactant: n=252 iNO only (control): n=259	Survival without BPD; 36 weeks, 31.3% vs. 31.7%, RB: 0.98, (95% CI: 0.75–1.28 P=0.89); 40 weeks, 58.7% vs. 54.1%, RB 1.08, (95% CI: 0.92–1.27 P=0.33). There was no difference in serious adverse events, comorbidities of prematurity, and the severity of lung disease to 36 weeks.
3	Hasan et al. 2017[9]	RCT	Canada	Multicenter (33 centers)	GA; <30 weeks Treatment; respiratory support on 5–14 days of age (n=451)	iNO: at 7 and 14 days of age iNO: n=175 N_2: n=175	Survival without BPD was not improved at 36 weeks. Respiratory and neurodevelopmental outcomes were not different at 18–24 months of postmenstrual age. There was no difference in the common complications of prematurity.
Studies investigating rescue iNO use for PH							
4	Truog et al. 2014[10]	Retrospective cohort	USA	Multicenter (13 centers)	GA; <29 weeks, BW; 400–1000 g (n=187)	iNO started at 7 days of age	iNO administration between days 7 and 14 was associated with an increased risk of BPD or death (OR: 2.24, 95%CI: 1.23–4.07). No information regarding complications or adverse events of iNO use was reported.
5	Hsiao et al. 2019[20]	Retrospective cohort	Taiwan	Single tertiary center	GA; 30.5 (26.0–36.5) weeks, BW; 1305 (788.5–2532) g, (n = 27)	Off-label use of iNO as "final rescue" for refractory hypoxemia (not for PPHN)	Common causes of off-label iNO use included BPD (19/27, 70.4%) and secondary PH (14/27, 51.9%) The Off-label iNO use group demonstrated the poorest response and the highest in-hospital mortality (P <0.001).

6	Nakanishi et al. 2023[4]	Retrospective cohort	Japan	Multicenter (NRNJ database)	GA; <28 weeks (n=462)	Post-acute iNO (iNO use in the late phase of hospitalization without PPHN)	Post-acute NO use increased in extremely preterm infants with more severe disease and complications. Post-acute NO was not associated with long-term neurodevelopmental outcomes at 3 years of age.
7	Oka et al. 2023[13]	Retrospective cohort	Japan	Single tertiary center	GA; <28 weeks, BW; 620 (482–814) g, (n=30)	iNO after 96 h of age (not for PPHN)	iNO thrombi-related adverse events were not reported. There was no difference in in-hospital outcomes between responders and non-responders. Methemoglobinemia (MetHb >5%) did not occur in any participants. Early iNO was associated with treatment response (OR: 0.89, 95% CI: 0.7970–0.995, P=0.04)
8	Fraga et al. 2023[14]	Prospective cohort	USA	Single tertiary center	GA; 25 weeks (24–27), (n=37)	iNO used at cGA ≥36 weeks, 40 weeks (37–43) at study entry (n=37)	Thirty (81%) patients had echocardiographic evidence of PAH before iNO, and 19 (56%) after 48 h of iNO (P=0.04). FiO_2 requirements were significantly different between time points, before initiation of iNO and after 48–168 h (P=0.05).
9	Nakao et al. 2012[21]	Retrospective cohort	Japan	Single tertiary center	GA; 24 weeks (22–28) BW 507.5 g (320–710 g) (n=12)	iNO used at ≥ 7 days	Indication; HRF with PH (n=10), CLD with PH (n=3) Outcome; Death (n=8) No complications were reported
10	Iwatani et al. 2022[22]	Retrospective cohort	Japan	Multicenter (10 centers)	GA; <28 weeks (23–27), BW; 417–1070 g (n=12)	iNO used at ≥ 7 days	Background; Histological CAM (n=9), SGA (<-3 SD) (n=2) Indication; CLD with PH (n=7), HRF with PH (n=5) Outcome; Death (n=8), HOT (n=3), tracheostomy (n=1)

iNO, inhaled nitric oxide; GA, gestational age; BW, birth weight; RB, relative benefit; CI, confidence interval; OR, odds ratio; BPD, bronchopulmonary dysplasia; RCT, randomized controlled trial; PH, pulmonary hypertension; HRF, hypoxic respiratory failure; LVEF, left ventricular ejection fraction; NRNJ, Neonatal Research Network of Japan; IQR, interquartile range; PAH; pulmonary artery hypertension, CLD; chronic lung disease, CAM; chorioamnionitis, SGA; small for gestational age, HOT; home oxygen therapy, LVEF; left ventricle ejection fraction, PPHN; persistent pulmonary hypertension of the newborn, MV; mechanical ventilation

Synthesis of results

Initiation criteria for post-acute iNO

The initiation criteria for post-acute iNO are poorly described in the literature; one of the most critical initiation criteria is echocardiographic diagnosis of PH, since NO acts specifically on pulmonary smooth muscle cells to decrease their tone, thus reducing pulmonary blood pressure. While the diagnostic criteria for PH are often poorly described in the literature, they are essential for the effective and safe administration of iNO in the post-acute phase. Among three studies focusing on iNO prophylaxis for BPD, none reported the diagnostic criteria for PH due to the nature of the studies.[8, 9, 11] However, in five studies examining the use of echocardiography to diagnose PH before iNO initiation, various criteria were reported.[12, 13, 14, 20, 22] Specifically, four studies identified ventricular septal wall flattening or bowing in the end-systole or pulmonary artery (PA) pressure elevation as indicators of PH.[12, 13, 14, 22] Fraga et al. further provided additional detailed echocardiographic findings for PH diagnosis, such as right-to-left shunting at the patent foramen ovale (PFO) or patent ductus arteriosus (PDA) level and the tricuspid peak velocity (TPV):right ventricular ejection time (RVET) ratio, as markers for PA pressure (PAP) elevation.[14] Accurate diagnosis of nitric-responsive PH, excluding conditions including left ventricular dysfunction, is critical. Echocardiography performed by a neonatologist before iNO initiation, as well as other multiple diagnostic criteria, should be considered crucial for the accurate and effective diagnosis of PH.

To measure the severity of respiratory compromise, various measures have been utilized. Three studies employed the respiratory severity index (mean airway pressure [MAP] × fraction of inspired oxygen [FiO_2]),[8, 11, 12] one utilized the OSI,[13] and two employed the oxygenation index.[12, 21] In out-of-concept studies, Hussein et al. reported the use of

echocardiography for PH diagnosis and noted echocardiographic findings, including flattened ventricular septum, tricuspid regurgitation (TR), and right-to-left shunt at the PFO/PDA level.[12] They also reported a 60% reduction in iNO use following the implementation of a weaning protocol.

A summary of these findings is presented in Table 3.

Table 3. Initiation criteria for iNO in all of the included studies

	Author	Initiation criteria for iNO			
		PH diagnosis	Echocardiographic findings	Surrogate marker of disease severity	Others
1	Ballard et al. 2006	N/A	N/A	MAP×FiO_2	N/A
2	Ballard et al. 2016	N/A	N/A	MAP×FiO_2	N/A
3	Hasan et al. 2017	N/A	N/A	N/A	N/A
4	Truog et al. 2014	N/A	N/A	N/A	N/A
5	Hsiao et al. 2019	Echocardiography	Details were not available	N/A	N/A
6	Nakanishi et al. 2023	N/A	N/A	N/A	N/A
7	Oka et al. 2023	Echocardiography (24%)	TR (PA>40 mmHg) D-shaped LV	OSI = MAP×FIO_2×100 /SpO_2	N/A
8	Fraga et al. 2023	Echocardiography	RV pressure >½ sSBP estimated from TRJV. Bidirectional or right-to-left shunting	N/A	N/A

			through a PDA. Septal flattening or bowing at end-systole. TPV:RVET ratio, 0.2–0.3, moderately elevated PAP; ≤0.2, significantly elevated PAP.		
9	Nakao et al. 2012	N/A	N/A	Oxygenation index	N/A
10	Iwatani et al. 2022	Cyanosis echocardiography	TR D-shaped LV	N/A	N/A

OSI, oxygen saturation index; pulmonary artery; TPV, tricuspid peak velocity; RVET, right ventricular ejection time; PAP, pulmonary artery pressure; MAP, mean airway pressure; FiO_2, fraction of inspired oxygen; TR, tricuspid regurgitation; iNO, inhaled nitric oxide; RV, right ventricle; LV, left ventricle; sSBP, systolic systemic blood pressure; PaO_2, partial pressure of oxygen; SpO_2, peripheral oxygen saturation; TRJV, tricuspid regurgitant jet velocity; HRF, hypoxic respiratory failure

Details of post-acute iNO administration

This section summarizes details of the post-acute iNO administration as outlined in the PCC framework, such as postnatal day of iNO initiation, dosage of iNO, duration of iNO therapy, discontinuation criteria of iNO therapy, concomitant use of other drugs, and adverse effects. The initiation day and duration of iNO administration varied widely, ranging from 2 to 314 days. The extended duration of iNO treatment may be attributed to its utilization as a rescue therapy in post-acute cases. Notably, three RCTs included a 24-day pre-protocol dosing period.[8, 9, 11] The criteria for discontinuation are not well-described. Regarding RCTs,[8, 9, 11] they were designated as protocol treatment. However, for rescue treatment, they

probably could not be stopped.[13, 14, 20, 21, 22] Additionally, for retrospective studies,[4,10] it may not be possible to retrieve these data. Hussain implemented a weaning protocol at their institution and successfully reduced the total iNO hours from 149 h to 59 h; however, the study was excluded from our review because it did not align with the study concept.[12]

The starting dose of iNO ranged from 3 to 20 ppm, with four studies starting at 20 ppm[8, 9, 11, 20] and one study reporting a maximum dose of 80 ppm.[20] Regarding adjunctive medications, reports involving the use of surfactants,[11, 13, 20] inotropes,[12, 20] corticosteroids,[13] bronchodilators,[14] and diuretics[14] were included. RCTs did not report significant differences in adverse events or increases in complications related to preterm birth,[8, 9, 11] which aligns with the findings of retrospective studies.[4, 12, 13, 21, 22] However, one case of pulmonary edema was reported after 48–168 h of iNO administration, without evidence of left ventricle dysfunction based on echocardiography.[14] A summary of these data is presented in Table 4.

Table 4. Summary of the details of post-acute iNO administration in preterm infants in the included studies

	Author Year	Postnatal day of iNO initiation	Dosage of iNO (ppm)	Duration of iNO	Other drugs	Discontinuation criteria	Adverse effects
1	Ballard et al. 2006	7–21 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	N/A	Specified by the protocol	No difference in the complications of prematurity No methemoglobinemia
2	Ballard et al. 2016	7–14 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	Surfactant	Specified by the protocol	No difference in severe adverse events and complications of prematurity
3	Hasan et al. 2017	7–14 days	Start with 20 ppm Decreased to 10 ppm in 72–96 h Then 5 ppm on day 10 or 11 Remain at 5 ppm until completion of therapy for 24 days	Minimum 24 days	N/A	Specified by the protocol	No differences in common complications of prematurity No elevation in NO_2 or methemoglobin level
4	Truog et al. 2014	7–28 days: (n=140 or 2.9%) >28 days: (n=47 or 0.96%)	N/A	N/A	N/A	N/A	N/A
5	Hsiao et al. 2019	> 7 days	Start with 20 ppm (rarely 10 ppm) Increased to 40 ppm without clinical response (max 80 ppm)	N/A	Surfactant 1/27 (3.7%) Dopamine 10/27 (37.0%) Dobutamine 6/27 (22.2%) Epinephrine 3/27 (11.1%) Milrinone 6/27 (22.2%)	N/A	N/A

6	Nakanishi et al. 2023	N/A (post-acute iNO; defined as iNO administration in the late phase of hospitalization)	N/A	26 days [14–70 days]	N/A	N/A	N/A
7	Oka et al. 2023	19 (11–26) days	Starting dose: 10 ppm	20.5 (8–32.5) days	Surfactant corticosteroid Bronchodilators; n=16 (43%)	N/A	No complications No methemoglobinemia
8	Fraga et al. 2023	40 weeks (37–43)	20 ppm	N/A	Diuretics; Furosemide: n=15 (40%), Chlorothiazide: n=16 (43%)	N/A	Pulmonary edema; n=1
9	Nakao et al. 2012	>7 days (214–2880 h)	Starting dose: 3–20 ppm Highest dose: 5–40 ppm	Median 130 h (22–1330 h)	N/A	N/A	No complications
10	Iwatani et al. 2022	39 (12–142) day	N/A	2–36 days	N/A	N/A	No methemoglobinemia No jaundice

iNO, inhaled nitric oxide

Studies investigating prophylactic iNO use for BPD

Three RCTs investigated the use of iNO administration to prevent the development of BPD.[8, 9, 11] All of these studies were multicenter and involved a relatively large number of patients, ranging from 451 to 582. The findings of these included studies are summarized in Table 2. All studies included in the analysis investigated survival without BPD as the primary outcome. Among them, only one study showed the efficacy of iNO within the treated group (relative benefit: 1.23, 95% confidence interval: 1.01–1.51, P=0.042),[8] while the remaining studies did not demonstrate improvement.[9, 11] None of the studies reported an increase in short-term outcomes or prematurity-associated comorbidities. Additionally, it is worth mentioning that although the study by Hasan enrolled newborns between 5 and 14 days of age, it did not specify when iNO therapy was initiated. Nevertheless, we included this study as it yielded significant findings, demonstrating no difference in respiratory or neurodevelopmental outcomes at 18 to 24 months postmenstrual age.[20]

Studies investigating rescue iNO use for HRF and PH

Seven studies focused on the use of iNO for rescue purposes. These studies comprised two database analyses,[4, 10] four retrospective cohort studies conducted in single tertiary centers,[13, 14, 20, 21] and one multicenter retrospective cohort study.[22] Additionally, we included two retrospective reports in Japanese, and summarized their results by extracting patient information that matched the study concept provided by the authors.[21, 22] The number of participants ranged from 12 to 462. A summary of these studies is presented in Table 2. Among these studies, four reported worse respiratory outcomes, and four reported death before discharge. Oka et al.[13] noted a positive response to post-acute iNO, defined as a >20% reduction in the oxygen saturation index (OSI), when introduced earlier. They also

found no difference in the incidence of in-hospital outcomes between responders and non-responders. Despite finding that two newborns received iNO treatment on day 6 of life and another on day 5, we included this study as the majority of the included newborns matched the inclusion criteria. Nakanishi et al.[4] reported in their retrospective cohort study using the Neonatal Research Network of Japan (NRNJ) database that there was no increase in developmental outcome at 3 years of age following post-acute iNO treatment. Fraga et al.[14] emphasized the importance of echocardiographic assessment of PH in infants with severe BPD before initiating iNO.

DISCUSSION

Summary of evidence

In this scoping review, a comprehensive screening of the English and Japanese literature from three databases published over two decades yielded 1518 reports. These studies were meticulously screened by at least two independent reviewers, focusing on the use of post-acute iNO for PH associated with BPD (BPD-PH) in preterm infants. Using the PCC framework, two distinct groups of reports were identified: one where iNO was utilized prophylactically to prevent development of BPD later, and another where iNO was used as a rescue therapy for preterm infants with BPD-PH.

Studies investigating prophylactic iNO use for BPD

In this subset of studies, patients were enrolled according to predefined protocols, with iNO administered as planned in terms of duration and dosage. While RCTs allowed for quantitative assessment, gathering clinical information on iNO use and associated complications or adverse events in preterm infants with BPD-PH posed challenges. One RCT published by Ballard et al. in 2006[8] demonstrated the effectiveness of post-acute iNO in

promoting survival without BPD, while two other studies did not show significant efficacy.[9, 11] Importantly, large prospective studies reported no adverse events with consistent iNO use.

Studies investigating rescue iNO use for PH

The seven reports in this category constituted the focal point of our review. These studies were retrospective in nature, primarily due to ethical constraints in conducting RCTs in patients with severe clinical courses, necessitating rescue treatment with iNO, especially given the lack of effective alternative therapies.

Among these studies, only a few have clearly described the indications for post-acute iNO use,[12, 14] with only three reports utilizing echocardiography as a criterion for diagnosis of PH.[13, 14, 22] However, the use of echocardiography as the gold standard for diagnosing PH varies among countries due to differences in available resources at the bedside.[7, 23] Nevertheless, to enhance the reliability of accumulated studies, quantitative evaluation using echocardiography is imperative, and should be incorporated into the diagnostic criteria for BPD-PH developed in the post-acute phase.

Employing large-scale multicenter studies or national data analyses, as demonstrated by Nakanishi et al.,[4] may help to overcome the challenges posed by the rarity of the study population and facilitate the acquisition of high-quality data.

Other findings

Among the studies mentioned above, we obtained valuable insights into clinical settings regarding the use of echocardiography as a diagnostic criterion for PH in the post-acute phase, information on the parameters used in the diagnostic procedure, and the practical utilization of iNO. Furthermore, we identified respiratory severity scores and OSI as potential surrogate parameters for assessing dyspnea. Considering the rare reporting of

complications and comorbidities associated with iNO use, the implementation of post-acute iNO appears to be safe.

Gaps

This scoping review underscores that the utilization of iNO to treat PH in the post-acute phase primarily occurs for rescue purposes. However, reports focusing on rescue purposes were predominantly retrospective, potentially biasing the inclusion of severe cases that led to adverse outcomes following iNO therapy. Additionally, due to the severity of oxygen desaturation in BPD-PH or HRF stemming from various causes, iNO may be initiated prior to a detailed evaluation of the PH status. Alternatively, although neonatologists in Japan implement bedside diagnostic echocardiography prior to administering iNO, this protocol may not be universally adhered to in other developed countries due to logistical issues, even though it is critical for PH diagnosis. Moreover, the clinical settings were not explicitly identified in this review due to insufficient data collection in each report. Another critical issue is the inter-rater variability associated with echocardiography, which needs to be addressed before its widespread adoption as a standard test. It is essential to promote the use of comprehensive echocardiographic evaluation for PH before administering iNO. While identifying a simple and robust parameter may help streamline the process, it is crucial to consider a holistic approach that encompasses multiple diagnostic criteria to ensure an accurate and effective diagnosis.

Strengths and limitations

To our knowledge, this is the first scoping review to explore the use of iNOs in post-acute settings. However, despite including some reports that did not fully align with our prespecified study concept, the information gathered on the diagnosis of PH was insufficient, leading to unsatisfactory results. The severity of PH associated with BPD

alongside the heterogeneity within the population, such as gestational age or the timing of iNO introduction, even in large-scale studies, further complicates efforts to enhance the quality of evidence regarding post-acute iNO administration. The failure to select patients with PH using echocardiography may be a key reason why the efficacy of post-acute iNO administration has not been convincingly demonstrated, which is a critical issue, given that iNO is a selective vasodilator.

Furthermore, ethical challenges hinder patient recruitment for RCTs examining the efficacy of post-acute iNO administration in patients with BPD-PH. Additionally, collecting comprehensive data, including diagnostic criteria for PH before iNO introduction in the post-acute phase, poses significant challenges in retrospective studies, especially when conducted on a large scale. To address these challenges, it is crucial to conduct prospectively registered cohort studies at the national level or report valuable information from large-scale single-center or multicenter studies. Notably, the low incidence of adverse events or complications associated with iNO use allows for a positive view regarding the introduction of post-acute iNO in preterm infants.

CONCLUSION

This scoping review sheds light on the clinical settings and current utilization of post-acute iNO therapy. Our results showed that the available evidence is insufficient to firmly support the use of post-acute iNO in treating infants with PH associated with BPD. Prospective studies with high-quality evidence are essential to address this knowledge gap. Additionally, given the severity and rarity of this disease, detailed retrospective studies are also warranted. We believe that accumulating evidence regarding the efficacy and safety of post-acute iNO in preterm infants will pave the way for its appropriate utilization as a promising gaseous agent in this population.

ACKNOWLEDGMENTS

We wish to express our sincere gratitude to Ms. Kuniko Sato, a librarian at St. Luke's International University, for her invaluable assistance in establishing the search strategy.

CONFLICT OF INTEREST

None declared.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. However, this study was supported by the Japan Society for Neonatal Health and Development. The supporting society had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

AUTHOR CONTRIBUTIONS

SK and HN conceptualized this study. All authors (SK, YM, MH, TN, SI, KH, AO, TH, MM, FN, MO, AN, SY, DS, EO, and HN) contributed to the scope and design of this review. DS and EO developed the search strategy through consultation with the medical librarian at St. Luke's International University, KS. SK, YM, MH, TN, and SI performed the screening, data charting, and data synthesis. SK prepared the first draft, and all other authors provided substantial input for the development of the final version. DS and HN provided feedback on the methodology. All authors (SK, YM, MH, TN, SI, KH, AO, TH, MM, FN, MO, AN, SY, DS, EO, and

HN) have read and revised the draft, and have approved the final version of the manuscript. SK is responsible for the overall content as a guarantor.

DATA SHARING STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

PATIENT CONSENT FOR PUBLICATION

Not applicable.

ETHICS APPROVAL

Obtaining an institutional review board approval is not required because of the nature of the methodology used in the analysis.

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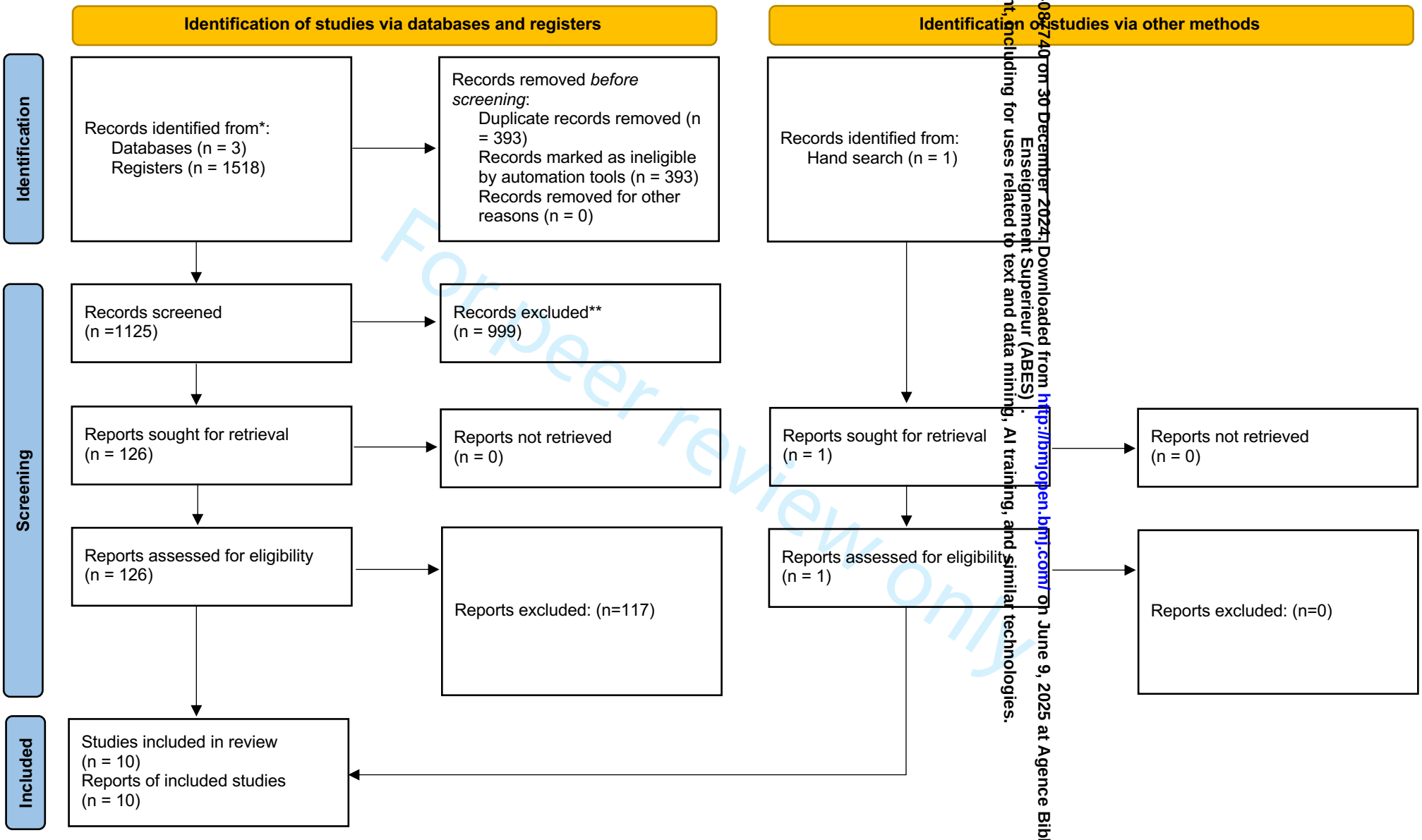
FIGURE LEGEND

Figure 1: Flow diagram showing the study selection process.

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Supplementary Appendix 1. Search strategy of the scoping review in Pubmed.

Search number	Query	Sort By	Filters	Search Details	Results
7	#4 and #5 and #6	Most Recent		("infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "pre term*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]) AND ("administration, inhalation"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "iNO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]) AND ("iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract]) AND ("english"[Language] OR "japanese"[Language]) AND 2022/12/01:2023/08/31[Date - Publication]	21
6	("2022/12/01"[Date - Publication] : "2023/08/31"[Date - Publication])	Most Recent		2022/12/01:2023/08/31[Date - Publication]	1,381,989
5	("english"[Language]) OR ("japanese"[Language])	Most Recent		"english"[Language] OR "japanese"[Language]	32,374,912
4	#1 and #2 and #3	Most Recent		("infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "pre term*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]) AND ("administration, inhalation"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "iNO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]) AND ("iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract])	715
3	iNO[tiab] OR "Nitrogen Monoxide"[tiab:~2] OR "Nitric Oxide"[mh] OR "nitric oxide"[tiab:~2] OR "nitric oxides"[tiab:~2] OR "no-inhalation"[tiab]	Most Recent		"iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract]	188,676
2	"Administration, Inhalation"[mh] OR "Administration, Intranasal"[mh] OR "Aerosols"[mh] OR Aerosol*[tiab] OR Atomizer*[tiab] OR Inhala*[tiab] OR inhale*[tiab] OR iNO[tiab] OR nasal[tiab] OR Nebulizer*[tiab] OR "Nebulizers and Vaporizers"[mh] OR "Respiratory Tract Absorption"[mh] OR Vaporizer*[tiab] OR "no-inhalation"[tiab]	Most Recent		"administration, inhalation"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "iNO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]	336,347
1	"Infant, Low Birth Weight"[mh] OR "Infant, Premature"[mh] OR "Infant, Premature, Diseases"[mh] OR LBW[tiab] OR low birth weight*[tiab] OR low birthweight*[tiab] OR "neonatal underweight"[tiab:~3] OR "neonatal under weight"[tiab:~3] OR Prematur*[tiab] OR Preterm*[tiab] OR pre-matur*[tiab] OR Pre-term*[tiab] OR "Premature Birth"[mh] OR VLBW[tiab]	Most Recent		"infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "pre term*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]	312,860

BMJ Open

Scoping review of initiation criteria for inhaled nitric oxide in preterm infants (born <34 weeks) after 7 days of age

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-087740.R3
Article Type:	Original research
Date Submitted by the Author:	25-Nov-2024
Complete List of Authors:	Kato, Shin; Japanese Red Cross Aichi Medical Center Nagoya Daiichi Hospital, Department of Pediatrics Minamitani, Yohei; Saitama Medical Center, Department of Pediatrics Hosokawa, Miku; Japanese Red Cross Medical Center, Department of Neonatology Nakashima, Toshinori; National Hospital Organization Kokura Medical Center, Department of Pediatrics Iwatani, Sota; Hyogo Prefectural Kobe Children's Hospital, Department of Neonatology Hirata, Katsuya; Osaka Women's and Children's Hospital, Department of Neonatal Medicine Oda, Arata; Nagano Children's Hospital, Division of Neonatology Hanita, Takushi; Tohoku University Hospital, Center for Perinatal and Neonatal Medicine Miyata, Masafumi; Fujita Health University, Department of Pediatrics Namba, Fumihiko; Saitama Medical Center, Department of Pediatrics Ochiai, Masayuki; Kyushu University, Research Center for Environmental and Developmental Medical Sciences Nakao, Atsushi; Japanese Red Cross Medical Center, Department of Neonatology Yoshimoto, Seiji; Hyogo Prefectural Kobe Children's Hospital, Department of Neonatology Suzuki, Daichi; Kanagawa Institute of Technology, Department of Nursing, Faculty of Health & Medical Sciences Ota, Erika; St. Luke's International University, Global School of Nursing Science, Global Health Nursing Nakanishi, Hidehiko; Kitasato University School of Medicine, Research and Development Center for New Medical Frontiers, Department of Advanced Medicine, Division of Neonatal Intensive Care Medicine
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	NEONATOLOGY, PAEDIATRICS, Pulmonary Disease < Lung Diseases

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Scoping review of initiation criteria for inhaled nitric oxide in preterm infants (born <34 weeks) after 7 days of age

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ABSTRACT

Objectives: Inhaled nitric oxide (iNO) is a known treatment for pulmonary hypertension (PH) associated with bronchopulmonary dysplasia in preterm infants after 7 days of age (post-acute phase). However, a consensus regarding the optimal criteria for initiating iNO therapy in this population in the post-acute phase is currently lacking. This study therefore aimed to identify the criteria for initiating iNO therapy, alongside the associated clinical and echocardiographic findings, in this population.

Design: We performed a scoping review using the population–concept–context framework following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.

Data sources: The PubMed, Embase, and the Japanese database "Ichushi" were systematically searched for relevant articles published between January 2003 and August 2023.

Eligibility criteria: This study included randomized controlled trials, prospective and retrospective cohort studies, case-control studies, and case series on iNO therapy in the post-acute phase for preterm infants born before 34 gestational weeks, written in English or Japanese.

Data extraction and synthesis: Data screening, extraction, and charting were performed independently, with the characteristics and findings of the included studies subsequently summarized.

Results: We included 10 reports that analyzed the data from 10 separate studies. The use of iNO therapy was categorized as prophylactic and rescue purpose. While randomized controlled trials and retrospective analyses indicated the safety of iNO during the post-acute

phase, the latter highlighted poor prognoses associated with severe cases requiring rescue iNO therapy. Additionally, although echocardiography is currently the primary diagnostic tool for identifying PH in preterm infants, standardized diagnostic criteria are lacking. Further, reports of complications and side effects associated with iNO are rare.

Conclusion: Our exploration of the initiation criteria for iNO revealed that definitive guidelines have not been established. Nonetheless, iNO administration during the post-acute phase appeared to be safe and devoid of complications.

Trial registration number: UMIN000051498.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.
- The protocol has been published to ensure transparency.
- We searched the Japanese database "Ichushi,'' which has documented a long history of active resuscitation of the most vulnerable preterm newborns.
- The review did not include a quality assessment of the included studies.

INTRODUCTION

Nitric oxide (NO) is a gaseous agent with a targeted effect on pulmonary hypertension (PH), significantly improving outcomes in newborns.[1, 2] In the United States, medical insurance limitations restrict the use of NO before 34 weeks of postmenstrual age. However, experience with inhaled NO (iNO) treatment has accumulated globally, with reports detailing its effect on both short- and long-term prognoses in premature newborns.[3, 4, 5] Bronchopulmonary dysplasia (BPD) significantly impacts pulmonary function and neurodevelopmental outcomes in premature newborns. Moderate-to-severe BPD is recognized as one of the key causes of hypoxic respiratory failure (HRF) or PH in newborns, particularly in the post-acute phase, which can be potentially fatal.[6, 7]

Notably, the efficacy of iNO during the post-acute phase has been documented for both BPD prevention and rescue from HRF or PH.[8, 9, 10] However, its effectiveness remains suboptimal. For example, iNO is not covered by medical insurance when initiated after the first week of life in Japan. Hence, it is imperative to establish evidence supporting its efficacy and broaden its indications to include the post-acute phase.

Despite the increasing off-label use of iNO, the criteria for its initiation vary across studies. Neonatologists have utilized diverse parameters to diagnose hypoxia, including oxygen saturation, arterial oxygen partial pressure, and the oxygenation index.[11, 12, 13] Similarly, various echocardiographic findings are used to diagnose PH.[7, 14] Echocardiography is considered the gold standard for PH diagnosis in newborns; however, logistical challenges may hinder its implementation prior to the initiation of iNO treatment in certain countries. Indeed, iNO is sometimes employed for clinical HRF or PH in the absence of any definitive echocardiographic findings, partly because of the aforementioned reasons. We believe that

the current perceived inadequacy of post-acute iNO therapy may be partly due to the enrollment of heterogeneous populations without a robust diagnosis of PH in prior studies investigating iNO efficacy.[15] In addition, while the mechanism of action of iNO renders it suitable for PH treatment, the optimal initiation criteria, particularly among premature infants in the post-acute phase, remain unclear.

Presently, there is a dearth of comprehensive information regarding the actual usage and initiation criteria for post-acute iNO in Japan and other nations. This review, therefore, aimed to provide a comprehensive overview of existing evidence on the administration of iNO after 7 days of life. It covers initiation criteria as well as dosage, duration, discontinuation criteria, concomitant use of other drugs, and adverse effects.

METHODS AND ANALYSIS

Protocol and registration

The protocol of this scoping review was registered at UMIN-CTR (registration number: UMIN000051498), and was subsequently published.[16] This review was conducted in compliance with the published protocol.

Eligibility criteria

This scoping review followed the Population-Concept-Context (PCC) framework outlined by the Joanna Briggs Institute (Table 1, https://doi.org/10.46658/JBIMES-20-12). We defined the post-acute phase as the late phase of primary hospitalization, i.e. after 7 days of life, based on the definition in previous nationwide surveys by Truog et al.[4] and Nakanishi et al.[6] We employed the 7th day of life as the transition point to exclude premature infants suffering from pulmonary hypertension of the newborn. Articles meeting the following

eligibility criteria were included: (1) articles enrolling preterm infants born at <34 weeks of gestation and aged >7 days; (2) provision of clinical information on iNO usage; (3) publication between January 2003 and August 2023; (4) conducted in developed countries; (5) written in English or Japanese; and (6) encompassing study designs such as randomized controlled trials (RCTs), prospective and retrospective cohort studies, case-control studies, and case series. We recruited preterm infants born at < 34 weeks of gestation because we have focused on pulmonary hypertension in the post-acute phase in newborns, a complication primarily observed in extremely preterm infants. To maintain the focus of our review, we narrowed our inclusion criteria by excluding the late preterm infants born between 34 to 36 weeks of gestation, as they rarely develop PH in their post-acute phase. The exclusion criteria were as follows: (1) participants with congenital malformation syndrome or chromosomal abnormalities; (2) animal and in vitro studies; and (3) conference abstracts, trial registrations, and protocol publications.

Table 1. PCC framework of this scoping review

Population	Preterm infants born at <34 weeks of gestation and treated with iNO after 7 days of age
Concept	Aim to identify the initiation criteria of iNO, postnatal day of the iNO initiation, dosage of iNO (ppm), duration of iNO therapy, discontinuation criteria of iNO therapy, concomitant use of other drugs, and adverse effects

	Published between January 2003 and August 2023
	Conducted in developed countries
	Published in English or Japanese
Context	Randomized controlled trial, cohort study, case-control study, and case series
	Excluding congenital malformation syndrome and a chromosomal abnormality

PCC, Population-Concept-Context; iNO, inhaled nitric oxide

Information sources

We conducted searches across PubMed and Embase, as well as the Japanese electronic bibliographic database "Ichushi." These searches were carried out by an accomplished librarian, supplemented by manual searches conducted by the authors. Given the paradigm shift in BPD to "new BPD" highlighted by Jobe in 1999,[17] alongside the advent of iNO in the clinical neonatology domain around 2000, we limited our search to studies published within the most recent two decades, spanning from January 2003 to August 2023. The search strategies are detailed in the Supplemental Appendix 1.

Selection of sources of evidence

Our scoping review approach adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist. (Supplemental Appendix 2)[18] The search results were deduplicated using EndNote 20, and imported into Rayyan, a web application,[19] to screen eligible studies. The authors (YM, MH, TN, and SI) independently evaluated the titles and abstracts of the identified studies using the PCC framework to ascertain potential eligibility based on the inclusion criteria.

Subsequently, a thorough full-text review of potentially eligible studies was performed. Any discrepancies regarding study eligibility were resolved through consensus discussion among the authors or adjudicated by another author's (SK) assessment. The study selection process is illustrated in the PRISMA flow diagram in Figure 1.

Data charting and synthesis of results

The characteristics of the included studies, including the study design, settings, populations, information regarding the provision of iNO therapy, efficacy of iNO therapy, complications, and other relevant findings, were systematically summarized in a pre-designed Excel form (Tables 2 to 4).

Critical appraisal of individual sources of evidence

Given the overarching objective of this scoping review to map existing evidence, an assessment of the risk of bias within the included studies was not undertaken.

Patient and public involvement

This study did not involve patients or members of the public, as only existing articles were analyzed. However, neonatologists participated in the review process and discussed the results.

RESULTS

Selection and characteristics of sources of evidence

A literature search was conducted on February 1, 2024, yielding 1518 records. Following deduplication, 393 duplicate records were removed. Subsequently, the remaining 1125 records underwent title and abstract screening, resulting in the exclusion of 999 records that did not meet the inclusion criteria. A full-text review of the remaining potentially

eligible studies was subsequently performed, leading to the exclusion of an additional 117 citations. Notably, one relevant Japanese study published in 2012 was identified through a manual literature search and included in the review. Ultimately, 10 original records were included in this study. The findings of these included studies are summarized in Table 2.

Table 2. Summary of the findings of the included studies

	Author Year	Study design	Country	Setting	Population	Intervention or Concept	Study findings
Studies investigating prophylactic iNO use for BPD							
1	Ballard et al. 2006[8]	RCT	USA	Multicenter (21 centers)	GA; ≤32 weeks BW; 500–1250 g on MV Treatment; 7 and 21 days of age (n=582).	iNO: n=294 N_2: n=288	Survival without BPD; 43.9% in NO and 36.8 % in placebo (RB: 1.2, 95% CI: 1.01–1.51, P=0.042) iNO group discharged sooner (P=0.04), shorter supplemental oxygen use (P=0.006). There were no short-term safety concerns and no difference in the complications of prematurity.
2	Ballard et al. 2016[11]	RCT	USA	Multicenter (25 centers)	GA; ≤28 weeks on MV Treatment; 7 and 14 days of age (n=511)	iNO+surfactant: n=252 iNO only (control): n=259	Survival without BPD; 36 weeks, 31.3% vs. 31.7%, RB: 0.98, (95% CI: 0.75–1.28 P=0.89); 40 weeks, 58.7% vs. 54.1%, RB 1.08, (95% CI: 0.92–1.27 P=0.33). There was no difference in serious adverse events, comorbidities of prematurity, and the severity of lung disease to 36 weeks.
3	Hasan et al. 2017[9]	RCT	Canada	Multicenter (33 centers)	GA; <30 weeks Treatment; respiratory support on 5–14 days of age (n=451)	iNO: at 7 and 14 days of age iNO: n=175 N_2: n=175	Survival without BPD was not improved at 36 weeks. Respiratory and neurodevelopmental outcomes were not different at 18–24 months of postmenstrual age. There was no difference in the common complications of prematurity.
Studies investigating rescue iNO use for PH							
4	Truog et al. 2014[10]	Retrospective cohort	USA	Multicenter (13 centers)	GA; <29 weeks, BW; 400–1000 g (n=187)	iNO started at 7 days of age	iNO administration between days 7 and 14 was associated with an increased risk of BPD or death (OR: 2.24, 95%CI: 1.23–4.07). No information regarding complications or adverse events of iNO use was reported.
5	Hsiao et al. 2019[20]	Retrospective cohort	Taiwan	Single tertiary center	GA; 30.5 (26.0–36.5) weeks, BW; 1305 (788.5–2532) g, (n = 27)	Off-label use of iNO as "final rescue" for refractory hypoxemia (not for PPHN)	Common causes of off-label iNO use included BPD (19/27, 70.4%) and secondary PH (14/27, 51.9%) The Off-label iNO use group demonstrated the poorest response and the highest in-hospital mortality (P <0.001).

6	Nakanishi et al. 2023[4]	Retrospective cohort	Japan	Multicenter (NRNJ database)	GA; <28 weeks (n=462)	Post-acute iNO (iNO use in the late phase of hospitalization without PPHN)	Post-acute NO use increased in extremely preterm infants with more severe disease and complications. Post-acute NO was not associated with long-term neurodevelopmental outcomes at 3 years of age.
7	Oka et al. 2023[13]	Retrospective cohort	Japan	Single tertiary center	GA; <28 weeks, BW; 620 (482–814) g, (n=30)	iNO after 96 h of age (not for PPHN)	iNO thrombi-related adverse events were not reported. There was no difference in in-hospital outcomes between responders and non-responders. Methemoglobinemia (MetHb >5%) did not occur in any participants. Early iNO was associated with treatment response (OR: 0.89, 95% CI: 0.7970–0.995, P=0.04)
8	Fraga et al. 2023[14]	Prospective cohort	USA	Single tertiary center	GA; 25 weeks (24–27), (n=37)	iNO used at cGA ≥36 weeks, 40 weeks (37–43) at study entry (n=37)	Thirty (81%) patients had echocardiographic evidence of PAH before iNO, and 19 (56%) after 48 h of iNO (P=0.04). FiO_2 requirements were significantly different between time points, before initiation of iNO and after 48–168 h (P=0.05).
9	Nakao et al. 2012[21]	Retrospective cohort	Japan	Single tertiary center	GA; 24 weeks (22–28) BW 507.5 g (320–710 g) (n=12)	iNO used at ≥ 7 days	Indication; HRF with PH (n=10), CLD with PH (n=3) Outcome; Death (n=8) No complications were reported
10	Iwatani et al. 2022[22]	Retrospective cohort	Japan	Multicenter (10 centers)	GA; <28 weeks (23–27), BW; 417–1070 g (n=12)	iNO used at ≥ 7 days	Background; Histological CAM (n=9), SGA (<-3 SD) (n=2) Indication; CLD with PH (n=7), HRF with PH (n=5) Outcome; Death (n=8), HOT (n=3), tracheostomy (n=1)

iNO, inhaled nitric oxide; GA, gestational age; BW, birth weight; RB, relative benefit; CI, confidence interval; OR, odds ratio; BPD, bronchopulmonary dysplasia; RCT, randomized controlled trial; PH, pulmonary hypertension; HRF, hypoxic respiratory failure; LVEF, left ventricular ejection fraction; NRNJ, Neonatal Research Network of Japan; IQR, interquartile range; PAH; pulmonary artery hypertension, CLD; chronic lung disease, CAM; chorioamnionitis, SGA; small for gestational age, HOT; home oxygen therapy, LVEF; left ventricle ejection fraction, PPHN; persistent pulmonary hypertension of the newborn, MV; mechanical ventilation

Synthesis of results

Initiation criteria for post-acute iNO

The initiation criteria for post-acute iNO are poorly described in the literature; one of the most critical initiation criteria is echocardiographic diagnosis of PH, since NO acts specifically on pulmonary smooth muscle cells to decrease their tone, thus reducing pulmonary blood pressure. While the diagnostic criteria for PH are often poorly described in the literature, they are essential for the effective and safe administration of iNO in the post-acute phase. Among three studies focusing on iNO prophylaxis for BPD, none reported the diagnostic criteria for PH due to the nature of the studies.[8, 9, 11] However, in five studies examining the use of echocardiography to diagnose PH before iNO initiation, various criteria were reported.[12, 13, 14, 20, 22] Specifically, four studies identified ventricular septal wall flattening or bowing in the end-systole or pulmonary artery (PA) pressure elevation as indicators of PH.[12, 13, 14, 22] Fraga et al. further provided additional detailed echocardiographic findings for PH diagnosis, such as right-to-left shunting at the patent foramen ovale (PFO) or patent ductus arteriosus (PDA) level and the tricuspid peak velocity (TPV):right ventricular ejection time (RVET) ratio, as markers for PA pressure (PAP) elevation.[14] Accurate diagnosis of nitric-responsive PH, excluding conditions including left ventricular dysfunction, is critical. Echocardiography performed by a neonatologist before iNO initiation, as well as other multiple diagnostic criteria, should be considered crucial for the accurate and effective diagnosis of PH.

To measure the severity of respiratory compromise, various measures have been utilized. Three studies employed the respiratory severity index (mean airway pressure [MAP] × fraction of inspired oxygen [FiO_2]),[8, 11, 12] one utilized the OSI,[13] and two employed the oxygenation index.[12, 21] In out-of-concept studies, Hussein et al. reported the use of

echocardiography for PH diagnosis and noted echocardiographic findings, including flattened ventricular septum, tricuspid regurgitation (TR), and right-to-left shunt at the PFO/PDA level.[12] They also reported a 60% reduction in iNO use following the implementation of a weaning protocol.

A summary of these findings is presented in Table 3.

Table 3. Initiation criteria for iNO in all of the included studies

	Author	Initiation criteria for iNO			
		PH diagnosis	Echocardiographic findings	Surrogate marker of disease severity	Others
1	Ballard et al. 2006	N/A	N/A	MAP×FiO_2	N/A
2	Ballard et al. 2016	N/A	N/A	MAP×FiO_2	N/A
3	Hasan et al. 2017	N/A	N/A	N/A	N/A
4	Truog et al. 2014	N/A	N/A	N/A	N/A
5	Hsiao et al. 2019	Echocardiography	Details were not available	N/A	N/A
6	Nakanishi et al. 2023	N/A	N/A	N/A	N/A
7	Oka et al. 2023	Echocardiography (24%)	TR (PA>40 mmHg) D-shaped LV	OSI = MAP×FIO_2×100 /SpO_2	N/A
8	Fraga et al. 2023	Echocardiography	RV pressure >½ sSBP estimated from TRJV. Bidirectional or right-to-left shunting	N/A	N/A

			through a PDA. Septal flattening or bowing at end-systole. TPV:RVET ratio, 0.2–0.3, moderately elevated PAP; ≤0.2, significantly elevated PAP.		
9	Nakao et al. 2012	N/A	N/A	Oxygenation index	N/A
10	Iwatani et al. 2022	Cyanosis echocardiography	TR D-shaped LV	N/A	N/A

OSI, oxygen saturation index; pulmonary artery; TPV, tricuspid peak velocity; RVET, right ventricular ejection time; PAP, pulmonary artery pressure; MAP, mean airway pressure; FiO_2, fraction of inspired oxygen; TR, tricuspid regurgitation; iNO, inhaled nitric oxide; RV, right ventricle; LV, left ventricle; sSBP, systolic systemic blood pressure; PaO_2, partial pressure of oxygen; SpO_2, peripheral oxygen saturation; TRJV, tricuspid regurgitant jet velocity; HRF, hypoxic respiratory failure

Details of post-acute iNO administration

This section summarizes details of the post-acute iNO administration as outlined in the PCC framework, such as postnatal day of iNO initiation, dosage of iNO, duration of iNO therapy, discontinuation criteria of iNO therapy, concomitant use of other drugs, and adverse effects. The initiation day and duration of iNO administration varied widely, ranging from 2 to 314 days. The extended duration of iNO treatment may be attributed to its utilization as a rescue therapy in post-acute cases. Notably, three RCTs included a 24-day pre-protocol dosing period.[8, 9, 11] The criteria for discontinuation are not well-described. Regarding RCTs,[8, 9, 11] they were designated as protocol treatment. However, for rescue treatment, they

probably could not be stopped.[13, 14, 20, 21, 22] Additionally, for retrospective studies,[4,10] it may not be possible to retrieve these data. Hussain implemented a weaning protocol at their institution and successfully reduced the total iNO hours from 149 h to 59 h; however, the study was excluded from our review because it did not align with the study concept.[12]

The starting dose of iNO ranged from 3 to 20 ppm, with four studies starting at 20 ppm[8, 9, 11, 20] and one study reporting a maximum dose of 80 ppm.[20] Regarding adjunctive medications, reports involving the use of surfactants,[11, 13, 20] inotropes,[12, 20] corticosteroids,[13] bronchodilators,[14] and diuretics[14] were included. RCTs did not report significant differences in adverse events or increases in complications related to preterm birth,[8, 9, 11] which aligns with the findings of retrospective studies.[4, 12, 13, 21, 22] However, one case of pulmonary edema was reported after 48–168 h of iNO administration, without evidence of left ventricle dysfunction based on echocardiography.[14] A summary of these data is presented in Table 4.

Table 4. Summary of the details of post-acute iNO administration in preterm infants in the included studies

	Author Year	Postnatal day of iNO initiation	Dosage of iNO (ppm)	Duration of iNO	Other drugs	Discontinuation criteria	Adverse effects
1	Ballard et al. 2006	7–21 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	N/A	Specified by the protocol	No difference in the complications of prematurity No methemoglobinemia
2	Ballard et al. 2016	7–14 days	Start with 20 ppm for 48–96 h Decreased to 10, 5, and 2 ppm at weekly intervals	Minimum 24 days	Surfactant	Specified by the protocol	No difference in severe adverse events and complications of prematurity
3	Hasan et al. 2017	7–14 days	Start with 20 ppm Decreased to 10 ppm in 72–96 h Then 5 ppm on day 10 or 11 Remain at 5 ppm until completion of therapy for 24 days	Minimum 24 days	N/A	Specified by the protocol	No differences in common complications of prematurity No elevation in NO_2 or methemoglobin level
4	Truog et al. 2014	7–28 days: (n=140 or 2.9%) >28 days: (n=47 or 0.96%)	N/A	N/A	N/A	N/A	N/A
5	Hsiao et al. 2019	> 7 days	Start with 20 ppm (rarely 10 ppm) Increased to 40 ppm without clinical response (max 80 ppm)	N/A	Surfactant 1/27 (3.7%) Dopamine 10/27 (37.0%) Dobutamine 6/27 (22.2%) Epinephrine 3/27 (11.1%) Milrinone 6/27 (22.2%)	N/A	N/A

6	Nakanishi et al. 2023	N/A (post-acute iNO; defined as iNO administration in the late phase of hospitalization)	N/A	26 days [14–70 days]	N/A	N/A	N/A
7	Oka et al. 2023	19 (11–26) days	Starting dose: 10 ppm	20.5 (8–32.5) days	Surfactant corticosteroid Bronchodilators; n=16 (43%)	N/A	No complications No methemoglobinemia
8	Fraga et al. 2023	40 weeks (37–43)	20 ppm	N/A	Diuretics; Furosemide: n=15 (40%), Chlorothiazide: n=16 (43%)	N/A	Pulmonary edema; n=1
9	Nakao et al. 2012	>7 days (214–2880 h)	Starting dose: 3–20 ppm Highest dose: 5–40 ppm	Median 130 h (22–1330 h)	N/A	N/A	No complications
10	Iwatani et al. 2022	39 (12–142) day	N/A	2–36 days	N/A	N/A	No methemoglobinemia No jaundice

iNO, inhaled nitric oxide

Studies investigating prophylactic iNO use for BPD

Three RCTs investigated the use of iNO administration to prevent the development of BPD.[8, 9, 11] All of these studies were multicenter and involved a relatively large number of patients, ranging from 451 to 582. The findings of these included studies are summarized in Table 2. All studies included in the analysis investigated survival without BPD as the primary outcome. Among them, only one study showed the efficacy of iNO within the treated group (relative benefit: 1.23, 95% confidence interval: 1.01–1.51, P=0.042),[8] while the remaining studies did not demonstrate improvement.[9, 11] None of the studies reported an increase in short-term outcomes or prematurity-associated comorbidities. Additionally, it is worth mentioning that although the study by Hasan enrolled newborns between 5 and 14 days of age, it did not specify when iNO therapy was initiated. Nevertheless, we included this study as it yielded significant findings, demonstrating no difference in respiratory or neurodevelopmental outcomes at 18 to 24 months postmenstrual age.[20]

Studies investigating rescue iNO use for HRF and PH

Seven studies focused on the use of iNO for rescue purposes. These studies comprised two database analyses,[4, 10] four retrospective cohort studies conducted in single tertiary centers,[13, 14, 20, 21] and one multicenter retrospective cohort study.[22] Additionally, we included two retrospective reports in Japanese, and summarized their results by extracting patient information that matched the study concept provided by the authors.[21, 22] The number of participants ranged from 12 to 462. A summary of these studies is presented in Table 2. Among these studies, four reported worse respiratory outcomes, and four reported death before discharge. Oka et al.[13] noted a positive response to post-acute iNO, defined as a >20% reduction in the oxygen saturation index (OSI), when introduced earlier. They also

found no difference in the incidence of in-hospital outcomes between responders and non-responders. Despite finding that two newborns received iNO treatment on day 6 of life and another on day 5, we included this study as the majority of the included newborns matched the inclusion criteria. Nakanishi et al.[4] reported in their retrospective cohort study using the Neonatal Research Network of Japan (NRNJ) database that there was no increase in developmental outcome at 3 years of age following post-acute iNO treatment. Fraga et al.[14] emphasized the importance of echocardiographic assessment of PH in infants with severe BPD before initiating iNO.

DISCUSSION

Summary of evidence

In this scoping review, a comprehensive screening of the English and Japanese literature from three databases published over two decades yielded 1518 reports. These studies were meticulously screened by at least two independent reviewers, focusing on the use of post-acute iNO for PH associated with BPD (BPD-PH) in preterm infants. Using the PCC framework, two distinct groups of reports were identified: one where iNO was utilized prophylactically to prevent development of BPD later, and another where iNO was used as a rescue therapy for preterm infants with BPD-PH.

Studies investigating prophylactic iNO use for BPD

In this subset of studies, patients were enrolled according to predefined protocols, with iNO administered as planned in terms of duration and dosage. While RCTs allowed for quantitative assessment, gathering clinical information on iNO use and associated complications or adverse events in preterm infants with BPD-PH posed challenges. One RCT published by Ballard et al. in 2006[8] demonstrated the effectiveness of post-acute iNO in

promoting survival without BPD, while two other studies did not show significant efficacy.[9, 11] Importantly, large prospective studies reported no adverse events with consistent iNO use.

Studies investigating rescue iNO use for PH

The seven reports in this category constituted the focal point of our review. These studies were retrospective in nature, primarily due to ethical constraints in conducting RCTs in patients with severe clinical courses, necessitating rescue treatment with iNO, especially given the lack of effective alternative therapies.

Among these studies, only a few have clearly described the indications for post-acute iNO use,[12, 14] with only three reports utilizing echocardiography as a criterion for diagnosis of PH.[13, 14, 22] However, the use of echocardiography as the gold standard for diagnosing PH varies among countries due to differences in available resources at the bedside.[7, 23] Nevertheless, to enhance the reliability of accumulated studies, quantitative evaluation using echocardiography is imperative, and should be incorporated into the diagnostic criteria for BPD-PH developed in the post-acute phase.

Employing large-scale multicenter studies or national data analyses, as demonstrated by Nakanishi et al.,[4] may help to overcome the challenges posed by the rarity of the study population and facilitate the acquisition of high-quality data.

Other findings

Among the studies mentioned above, we obtained valuable insights into clinical settings regarding the use of echocardiography as a diagnostic criterion for PH in the post-acute phase, information on the parameters used in the diagnostic procedure, and the practical utilization of iNO. Furthermore, we identified respiratory severity scores and OSI as potential surrogate parameters for assessing dyspnea. Considering the rare reporting of

complications and comorbidities associated with iNO use, the implementation of post-acute iNO appears to be safe.

Gaps

This scoping review underscores that the utilization of iNO to treat PH in the post-acute phase primarily occurs for rescue purposes. However, reports focusing on rescue purposes were predominantly retrospective, potentially biasing the inclusion of severe cases that led to adverse outcomes following iNO therapy. Additionally, due to the severity of oxygen desaturation in BPD-PH or HRF stemming from various causes, iNO may be initiated prior to a detailed evaluation of the PH status. Alternatively, although neonatologists in Japan implement bedside diagnostic echocardiography prior to administering iNO, this protocol may not be universally adhered to in other developed countries due to logistical issues, even though it is critical for PH diagnosis. Moreover, the clinical settings were not explicitly identified in this review due to insufficient data collection in each report. Another critical issue is the inter-rater variability associated with echocardiography, which needs to be addressed before its widespread adoption as a standard test. It is essential to promote the use of comprehensive echocardiographic evaluation for PH before administering iNO. While identifying a simple and robust parameter may help streamline the process, it is crucial to consider a holistic approach that encompasses multiple diagnostic criteria to ensure an accurate and effective diagnosis.

Strengths and limitations

To our knowledge, this is the first scoping review to explore the use of iNOs in post-acute settings. However, despite including some reports that did not fully align with our prespecified study concept, the information gathered on the diagnosis of PH was insufficient, leading to unsatisfactory results. The severity of PH associated with BPD

alongside the heterogeneity within the population, such as gestational age or the timing of iNO introduction, even in large-scale studies, further complicates efforts to enhance the quality of evidence regarding post-acute iNO administration. The failure to select patients with PH using echocardiography may be a key reason why the efficacy of post-acute iNO administration has not been convincingly demonstrated, which is a critical issue, given that iNO is a selective vasodilator.

Furthermore, ethical challenges hinder patient recruitment for RCTs examining the efficacy of post-acute iNO administration in patients with BPD-PH. Additionally, collecting comprehensive data, including diagnostic criteria for PH before iNO introduction in the post-acute phase, poses significant challenges in retrospective studies, especially when conducted on a large scale. To address these challenges, it is crucial to conduct prospectively registered cohort studies at the national level or report valuable information from large-scale single-center or multicenter studies. Notably, the low incidence of adverse events or complications associated with iNO use allows for a positive view regarding the introduction of post-acute iNO in preterm infants.

CONCLUSION

This scoping review sheds light on the clinical settings and current utilization of post-acute iNO therapy. Our results showed that the available evidence is insufficient to firmly support the use of post-acute iNO in treating infants with PH associated with BPD. Prospective studies with high-quality evidence are essential to address this knowledge gap. Additionally, given the severity and rarity of this disease, detailed retrospective studies are also warranted. We believe that accumulating evidence regarding the efficacy and safety of post-

acute iNO in preterm infants will pave the way for its appropriate utilization as a promising gaseous agent in this population.

ACKNOWLEDGMENTS

We wish to express our sincere gratitude to Ms. Kuniko Sato, a librarian at St. Luke's International University, for her invaluable assistance in establishing the search strategy.

CONFLICT OF INTEREST

None declared.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. However, this study was supported by the Japan Society for Neonatal Health and Development. The supporting society had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

AUTHOR CONTRIBUTIONS

SK and HN conceptualized this study. All authors (SK, YM, MH, TN, SI, KH, AO, TH, MM, FN, MO, AN, SY, DS, EO, and HN) contributed to the scope and design of this review. DS and EO developed the search strategy through consultation with the medical librarian at St. Luke's International University, KS. SK, YM, MH, TN, and SI performed the screening, data charting, and data synthesis. SK prepared the first draft, and all other authors provided substantial

input for the development of the final version. DS and HN provided feedback on the methodology. All authors (SK, YM, MH, TN, SI, KH, AO, TH, MM, FN, MO, AN, SY, DS, EO, and HN) have read and revised the draft, and have approved the final version of the manuscript. SK is responsible for the overall content as a guarantor.

DATA SHARING STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

PATIENT CONSENT FOR PUBLICATION

Not applicable.

ETHICS APPROVAL

Obtaining an institutional review board approval is not required because of the nature of the methodology used in the analysis.

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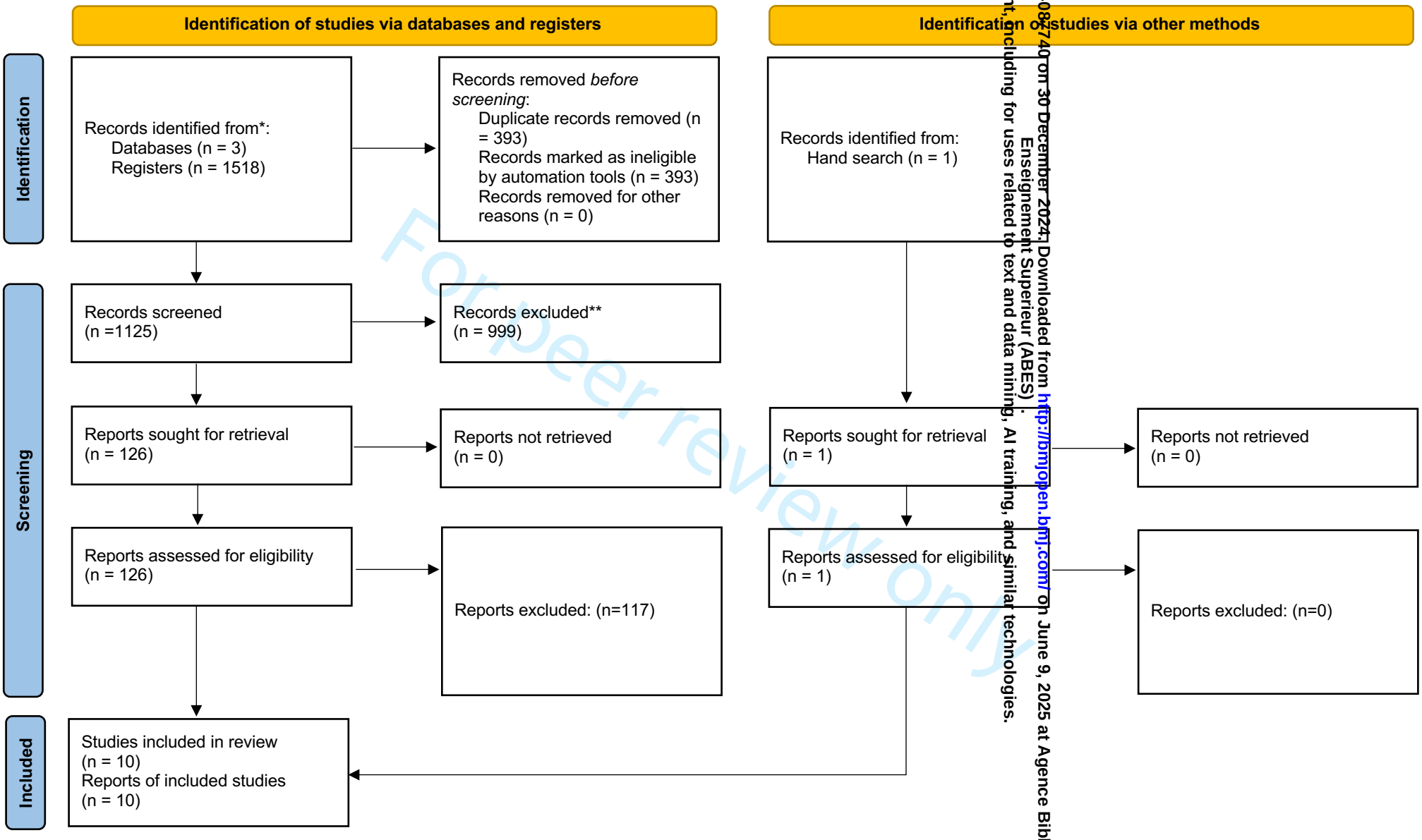
FIGURE LEGEND

Figure 1: Flow diagram showing the study selection process.

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Supplementary Appendix 1. Search strategy of the scoping review in Pubmed.

Search number	Query	Sort By	Filters	Search Details	Results
7	#4 and #5 and #6	Most Recent		("infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "pre term*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]) AND ("administration, inhalation"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "iNO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]) AND ("iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract]) AND ("english"[Language] OR "japanese"[Language]) AND 2022/12/01:2023/08/31[Date - Publication]	21
6	("2022/12/01"[Date - Publication] : "2023/08/31"[Date - Publication])	Most Recent		2022/12/01:2023/08/31[Date - Publication]	1,381,989
5	("english"[Language]) OR ("japanese"[Language])	Most Recent		"english"[Language] OR "japanese"[Language]	32,374,912
4	#1 and #2 and #3	Most Recent		("infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "pre term*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]) AND ("administration, inhalation"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "iNO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]) AND ("iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract])	715
3	iNO[tiab] OR "Nitrogen Monoxide"[tiab:~2] OR "Nitric Oxide"[mh] OR "nitric oxide"[tiab:~2] OR "nitric oxides"[tiab:~2] OR "no-inhalation"[tiab]	Most Recent		"iNO"[Title/Abstract] OR "Nitrogen Monoxide"[Title/Abstract:~2] OR "Nitric Oxide"[MeSH Terms] OR "Nitric Oxide"[Title/Abstract:~2] OR "nitric oxides"[Title/Abstract:~2] OR "no-inhalation"[Title/Abstract]	188,676
2	"Administration, Inhalation"[mh] OR "Administration, Intranasal"[mh] OR "Aerosols"[mh] OR Aerosol*[tiab] OR Atomizer*[tiab] OR Inhala*[tiab] OR inhale*[tiab] OR iNO[tiab] OR nasal[tiab] OR Nebulizer*[tiab] OR "Nebulizers and Vaporizers"[mh] OR "Respiratory Tract Absorption"[mh] OR Vaporizer*[tiab] OR "no-inhalation"[tiab]	Most Recent		"administration, inhalation"[MeSH Terms] OR "administration, intranasal"[MeSH Terms] OR "Aerosols"[MeSH Terms] OR "aerosol*"[Title/Abstract] OR "atomizer*"[Title/Abstract] OR "inhala*"[Title/Abstract] OR "inhale*"[Title/Abstract] OR "iNO"[Title/Abstract] OR "nasal"[Title/Abstract] OR "nebulizer*"[Title/Abstract] OR "Nebulizers and Vaporizers"[MeSH Terms] OR "Respiratory Tract Absorption"[MeSH Terms] OR "vaporizer*"[Title/Abstract] OR "no-inhalation"[Title/Abstract]	336,347
1	"Infant, Low Birth Weight"[mh] OR "Infant, Premature"[mh] OR "Infant, Premature, Diseases"[mh] OR LBW[tiab] OR low birth weight*[tiab] OR low birthweight*[tiab] OR "neonatal underweight"[tiab:~3] OR "neonatal under weight"[tiab:~3] OR Prematur*[tiab] OR Preterm*[tiab] OR pre-matur*[tiab] OR Pre-term*[tiab] OR "Premature Birth"[mh] OR VLBW[tiab]	Most Recent		"infant, low birth weight"[MeSH Terms] OR "infant, premature"[MeSH Terms] OR "infant, premature, diseases"[MeSH Terms] OR "LBW"[Title/Abstract] OR "low birth weight*"[Title/Abstract] OR "low birthweight*"[Title/Abstract] OR "neonatal underweight"[Title/Abstract:~3] OR "neonatal under weight"[Title/Abstract:~3] OR "prematur*"[Title/Abstract] OR "preterm*"[Title/Abstract] OR "pre matur*"[Title/Abstract] OR "pre term*"[Title/Abstract] OR "Premature Birth"[MeSH Terms] OR "VLBW"[Title/Abstract]	312,860