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

Shin Kato ,[1] Yohei Minamitani,[2] Miku Hosokawa,[3] Toshinori Nakashima,[4] Sota Iwatani ,[5] Katsuya Hirata ,[6] Arata Oda,[7] Takushi Hanita,[8] Masafumi Miyata,[9] Fumihiko Namba,[2] Masayuki Ochiai,[10] Atsushi Nakao,[3] Seiji Yoshimoto,[5] Daichi Suzuki,[11,12] Erika Ota ,[12] Hidehiko Nakanishi,[13] on behalf of the Japan Society for Neonatal Health and Development

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For numbered affiliations see end of article.

Correspondence to
Dr Shin Kato;
shinkato2@gmail.com

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 (postacute phase). However, a consensus regarding the optimal criteria for initiating iNO therapy in this population in the postacute 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 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 randomised controlled trials, prospective and retrospective cohort studies, case–control studies and case series on iNO therapy in the postacute 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 summarised.

Results We included 10 reports that analysed the data from 10 separate studies. The use of iNO therapy was categorised as prophylactic and rescue purposes. While randomised controlled trials (RCTs) and retrospective analyses indicated the safety of iNO during the postacute 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, standardised 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 postacute phase appeared to be safe and devoid of complications.

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.

Trial registration number UMIN000051498.

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 USA, 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-term and long-term prognoses in premature newborns.[3–5] Bronchopulmonary dysplasia (BPD) significantly impacts pulmonary function and neurodevelopmental outcomes in premature newborns. Moderate-to-severe BPD is recognised as one of the key causes of hypoxic respiratory failure (HRF) or PH in newborns, particularly in the postacute phase, which can be potentially fatal.[6 7]

Notably, the efficacy of iNO during the postacute phase has been documented for both BPD prevention and rescue from HRF or PH.[8–10] 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 postacute phase.

Despite the increasing off-label use of iNO, the criteria for its initiation vary across studies. Neonatologists have used diverse parameters to diagnose hypoxia, including oxygen saturation, arterial oxygen partial pressure and the oxygenation index.[11–13] 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 postacute iNO therapy may be partly due to the enrolment 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 postacute phase, remain unclear.

Presently, there is a dearth of comprehensive information regarding the actual usage and initiation criteria for postacute 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 postacute phase as the late phase of primary hospitalisation, that is, after 7 days of life, based on the definition in previous nationwide surveys by Truog *et al*[10] and Nakanishi *et al*.[4] We employed the seventh day of life as the transition point to exclude premature infants suffering from PH 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 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 PH in the postacute 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 and 36 weeks of gestation, as they rarely develop PH in their postacute 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
Context	Published between January 2003 and August 2023 Conducted in developed countries Published in English or Japanese Randomised controlled trial, cohort study, case–control study and case series Excluding congenital malformation syndrome and a chromosomal abnormality

iNO, inhaled nitric oxide; PCC, Population-Concept-Context; ppm, parts per million.

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 online supplemental appendix 1.

Selection of sources of evidence

Our scoping review approach adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for Scoping Reviews Checklist (online supplemental appendix 2).[18] The search results were deduplicated using EndNote V.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

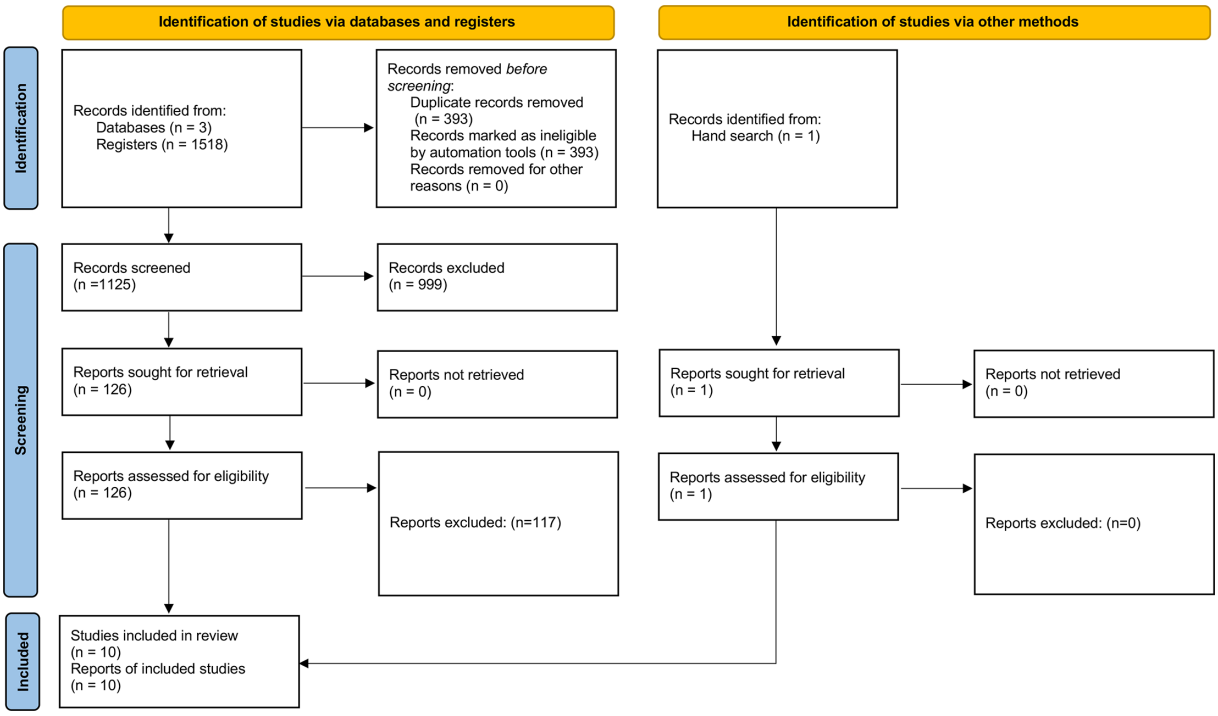

Figure 1 Flow diagram showing the study selection process. From: Page *et al*.[24]

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 summarised in a predesigned Excel form (tables 2–4).

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 analysed. 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 1 February 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 summarised in table 2.

Synthesis of results

Initiation criteria for postacute iNO

The initiation criteria for postacute 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 postacute 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.[12–14 20 21] Specifically, four studies identified ventricular septal wall flattening or bowing in the end-systole or pulmonary artery (PA) pressure elevation as indicators of PH.[12–14 21] 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:right ventricular ejection time ratio, as markers for PA pressure elevation.[14] Accurate diagnosis of nitric-responsive PH, excluding conditions including left ventricular dysfunction, is critical. Echocardiography performed by a neonatologist before

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	Multicentre (21 centres)	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 to 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	Multicentre (25 centres)	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 to 1.28 p=0.89); 40 weeks, 58.7% vs 54.1%, RB: 1.08, (95% CI: 0.92 to 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	Multicentre (33 centres)	GA; <30 weeks treatment; respiratory support at 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	Multicentre (13 centres)	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 to 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 centre	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 hypoxaemia (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	Multicentre (NRNJ database)	GA; <28 weeks (n=462)	Postacute iNO (iNO use in the late phase of hospitalisation without PPHN)	Postacute iNO use increased in extremely preterm infants with more severe disease and complications. Postacute 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 centre	GA; <28 weeks, BW; 620 (482–814) g, (n=30)	iNO after 96 hours of age (not for PPHN)	iNO thrapy-related adverse events were not reported. There was no difference in in-hospital outcomes between responders and non-responders. Methaemoglobinaemia (MetHb >5%) did not occur in any participant. Early iNO was associated with treatment response (OR: 0.89, 95% CI: 0.7970 to 0.995, p=0.04)
8	Fraga *et al*, 2023[14]	Prospective cohort	USA	Single tertiary centre	GA; 25 weeks (24–27), (n=37)	iNO used at cGA≥36 weeks, 40 weeks (37–43) at study entry (n=37)	30 (81%) patients had echocardiographic evidence of PAH before iNO, and 19 (56%) after 48 hours of iNO (p=0.04). FiO_2 requirements were significantly different between time points, before initiation of iNO and after 48–168 hour (p=0.05).
9	Nakao *et al*, 2012[22]	Retrospective cohort	Japan	Single tertiary centre	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

Continued

Table 2 Continued

	Author year	Study design	Country	Setting	Population	Intervention or concept	Study findings
10	Iwatani *et al*, 2022[21]	Retrospective cohort	Japan	Multicentre (10 centres)	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)

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

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 used. Three studies employed the respiratory severity index (mean airway pressure×fraction of inspired oxygen),[8 11 12] one used the OSI[13] and two employed the oxygenation index.[12 22] In out-of-concept studies, Hussain *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.

Details of postacute iNO administration

This section summarises details of the postacute 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 utilisation as a rescue therapy in postacute cases. Notably, three RCTs included a 24-day preprotocol 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 20–22] Additionally, for retrospective studies,[4 10] it may not be possible to retrieve these

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

		Initiation criteria for iNO			
	Author	PH diagnosis	Echocardiographic findings	Surrogate marker of disease severity	Others
1	Ballard *et al*, 2006[8]	N/A	N/A	MAP×FiO_2	N/A
2	Ballard *et al*, 2016[11]	N/A	N/A	MAP×FiO_2	N/A
3	Hasan *et al*, 2017[9]	N/A	N/A	N/A	N/A
4	Truog *et al*, 2014[10]	N/A	N/A	N/A	N/A
5	Hsiao *et al*, 2019[20]	Echocardiography	Details were not available	N/A	N/A
6	Nakanishi *et al*, 2023[4]	N/A	N/A	N/A	N/A
7	Oka *et al*, 2023[13]	Echocardiography (24%)	TR (PA >40 mmHg) D-shaped LV	OSI=MAP×FIO_2×100/SpO_2	N/A
8	Fraga *et al*, 2023[14]	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[22]	N/A	N/A	Oxygenation index	N/A
10	Iwatani *et al*, 2022[21]	Cyanosis echocardiography	TR D-shaped LV	N/A	N/A

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

Table 4 Summary of the details of postacute 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[8]	7–21 days	Start with 20 ppm for 48–96 hours 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 methaemoglobinaemia
2	Ballard *et al*, 2016[11]	7–14 days	Start with 20 ppm for 48–96 hours 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[9]	7–14 days	Start with 20 ppm Decreased to 10 ppm in 72–96 hours 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 methaemoglobin level
4	Truog *et al*, 2014[10]	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[20]	>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[4]	N/A (postacute iNO; defined as iNO administration in the late phase of hospitalisation)	N/A	26 days (14–70 days)	N/A	N/A	N/A
7	Oka *et al*, 2023[13]	19 (11–26) days	Starting dose: 10 ppm	20.5 (8–32.5) days	Surfactant corticosteroid	N/A	No complications No methaemoglobinaemia
8	Fraga *et al*, 2023[14]	40 weeks (37–43)	20 ppm	N/A	Bronchodilators; n=16 (43%) Diuretics; furosemide: n=15 (40%), chlorothiazide: n=16 (43%)	N/A	Pulmonary oedema; n=1
9	Nakao *et al*, 2012[22]	>7 days (214–2880 hours)	Starting dose: 3–20 ppm Highest dose: 5–40 ppm	Median 130 hours (22–1330 hours)	N/A	N/A	No complications
10	Iwatani *et al*, 2022[21]	39 (12–142) days	N/A	2–36 days	N/A	N/A	No methaemoglobinaemia No jaundice

iNO, inhaled nitric oxide; ppm, parts per million.

data. Hussain *et al* implemented a weaning protocol at their institution and successfully reduced the total iNO hours from 149 hours to 59 hours; 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 oedema was reported after 48–168 hours of iNO administration, without evidence of left ventricle dysfunction based on echocardiography.[14] A summary of these data is presented in table 4.

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 multicentre and involved a relatively large number of patients, ranging from 451 to 582. The findings of these included studies are summarised 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% CI 1.01 to 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 *et al* 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 18–24 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 centres,[13 14 20 22] and one multicentre retrospective cohort study.[21] Additionally, we included two retrospective reports in Japanese and summarised 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 database that there was no increase in developmental outcome at 3 years of age following postacute iNO treatment. Fraga *et al*[14] emphasised 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 postacute 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 used prophylactically to prevent the 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*[8] demonstrated the effectiveness of postacute 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 using echocardiography as a criterion for diagnosis of PH.[13 14 21] 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 postacute phase.

Employing large-scale multicentre 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 postacute phase, information on the parameters used in the diagnostic procedure, and the practical utilisation of iNO. Furthermore, we identified respiratory severity scores and OSI as potential surrogate parameters for assessing dyspnoea. Considering the rare reporting of complications and comorbidities associated with iNO use, the implementation of postacute iNO appears to be safe.

Gaps

This scoping review underscores that the utilisation of iNO to treat PH in the postacute 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 postacute 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 postacute iNO administration. The failure to select patients with PH using echocardiography may be a key reason why the efficacy of postacute 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 postacute iNO administration in patients with BPD-PH. Additionally, collecting comprehensive data, including diagnostic criteria for PH before iNO introduction in the postacute 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-centre or multicentre studies. Notably, the low incidence of adverse events or complications associated with iNO use allows for a positive view regarding the introduction of postacute iNO in preterm infants.

CONCLUSION

This scoping review sheds light on the clinical settings and current utilisation of postacute iNO therapy. Our results showed that the available evidence is insufficient to firmly support the use of postacute 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 postacute iNO in preterm infants will pave the way for its appropriate utilisation as a promising gaseous agent in this population.

Author affiliations
[1]Department of Pediatrics, Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital, Nagoya, Aichi, Japan
[2]Department of Pediatrics, Saitama Medical Center, Saitama Medical University, Kawagoe, Saitama, Japan
[3]Department of Neonatology, Japanese Red Cross Medical Center, Shibuya, Tokyo, Japan
[4]Department of Pediatrics, National Hospital Organization Kokura Medical Center, Kitakyushu, Fukuoka, Japan
[5]Department of Neonatology, Hyogo Prefectural Kobe Children's Hospital, Kobe, Hyogo, Japan
[6]Department of Neonatal Medicine, Osaka Women's and Children's Hospital, Izumi, Osaka, Japan
[7]Division of Neonatology, Nagano Children's Hospital, Azumino, Nagano, Japan
[8]Center for Perinatal and Neonatal Medicine, Tohoku University Hospital, Sendai, Miyagi, Japan
[9]Department of Pediatrics, Fujita Health University, Toyoake, Aichi, Japan
[10]Research Center for Environmental and Developmental Medical Sciences, Kyushu University, Fukuoka, Fukuoka, Japan
[11]Department of Nursing, Faculty of Health & Medical Sciences, Kanagawa Institute of Technology, Atsugi, Kanagawa, Japan
[12]Global Health Nursing, Graduate School of Nursing Science, St. Luke's International University, Chuo-ku, Tokyo, Japan
[13]Research and Development Center for New Medical Frontiers, Department of Advanced Medicine, Division of Neonatal Intensive Care Medicine, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan

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ORCID iDs
Shin Kato http://orcid.org/0000-0002-8136-7044
Sota Iwatani http://orcid.org/0000-0002-2871-4000
Katsuya Hirata http://orcid.org/0000-0003-3148-9892
Erika Ota http://orcid.org/0000-0002-3945-7441

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