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Title page

Title: Standardization of nitric oxide inhalation in extremely preterm infants in Japan

Short title: a nationwide survey of iNO in preterm infants

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ABSTRACT

Background

In perinatal medicine, inhaled nitric oxide (iNO) has been an important tool for the treatment of full-term and late-preterm infants with persistent pulmonary hypertension of the newborn (PPHN) and hypoxemic respiratory failure (HRF). However, its use in more premature infants is controversial. To evaluate the current clinical practices regarding use of acute inhaled nitric oxide (iNO) therapy in extremely preterm infants, a nationwide survey was conducted in Japan.

Methods

A questionnaire survey was conducted from May to September, 2015.

Questionnaires about PPHN and iNO treatment were sent to the doctor in charge of the neonatal care unit in 213 perinatal medical centers (PMCs) that possessed iNO equipment in Japan.

Results

A total of 143 of the 213 PMCs provided responses (67.1%). A diagnosis of PPHN was made exclusively by echocardiography in all PMCs. On determination of definitive PPHN diagnosis, iNO was selected in the majority of the PMCs (72%) and started from ≤ 10 ppm in the most of PMCs (49.7%) for extremely preterm infants. During iNO therapy, cardiac function was checked with echocardiography by a neonatologist every ~8 hours. Weaning of iNO treatment was started when differential SpO2 disappeared, SPO2 reached 100%, etc. After iNO concentration reached 5 ppm, it was decreased gradually and carefully in five steps, taking 12 – 24 hours to go from 5 to 0 ppm.

Conclusions

This survey indicated that iNO was predominantly used in extremely preterm infants as early rescue therapy for PPHN based on echocardiography findings performed by a neonatologist .

Key words: low birth weight, persistent pulmonary hypertension of the newborn, respiratory distress syndrome, echocardiography

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is characterized clinically by hypoxemic respiratory failure (HRF). PPHN involves failure of extrauterine adaptation and continued elevation of pulmonary vascular resistance, and is associated with high risks of mortality and morbidity.[1] In perinatal medicine, inhaled nitric oxide (iNO) was initially studied for its pulmonary vasodilating effects in infants with pulmonary hypertension (PH) and has since become an important treatment modality for full-term and late-preterm infants with PPHN and HRF.[2,3] In animal models of neonatal chronic lung disease (CLD), iNO was shown to stimulate angiogenesis, augment alveolarization, improve surfactant function, and inhibit proliferation of smooth muscle cells and abnormal elastin deposition.[4-8]

In preterm infants respiratory distress syndrome (RDS) may be worsened by the concurrent development of right-to-left extrapulmonary shunting due to pulmonary hypertension, [9,10] or intrapulmonary shunting due to poor ventilation-perfusion matching. [11] Therefore, it has been suggested that inhaled nitric oxide may acutely improve oxygenation in these patients due to its vasodilatory effect by lowering pulmonary vascular resistance and/or contributing to a better distribution of pulmonary blood flow.[12]

However, its use in preterm infants (gestational age (GA) ≤ 34 weeks) is controversial.

A consensus of the US National Institute of Health (NIH) [13] suggests that the effectiveness of iNO therapy should be further studied in more select preterm infants, such as those with PPHN who need prolonged mechanical ventilation.

In Japan, iNO therapy is covered by national medical insurance for HRF associated with PH in the neonatal period regardless of gestational age. Post-marketing surveillance by a company offering iNO therapy indicated that it has been used safely in many extremely preterm infants,[14] with mortality rates of 22.2% in infants born at GA < 28 weeks , 32.4% in those born at GA 29–33 weeks, and 22.2% in late-preterm infants (born at GA 34 – 36 weeks). On the other hand, there have been few nationwide studies regarding the treatment of iNO in extremely preterm infants in Japan.

Study objective

This study was performed to gather information on the current clinical practices regarding the use of acute iNO therapy in extremely preterm (GA < 28 weeks) infants, especially with regard to the indications, dosage, monitoring, and weaning strategies in Japan. Standardization of rescue use of iNO

treatment for extremely preterm infants is proposed. Treatment in the chronic phase (i.e. PH of CLD) was excluded from the study.

Methods

Questionnaires were sent by mail or e-mail to the doctor in charge of the neonatal care unit at each of 213 perinatal medical centers (PMCs) that possessed iNO equipment between May and September, 2015. There is a register of nurseries in a company (AIR WATER INC.) offering iNO therapy in Japan. Information was collected on management of PH, indications, dosage, and weaning of iNO therapy in both term and extremely preterm infants administered iNO at postnatal age < 4 weeks.

Some questions had multiple choices and respondents were allowed to select one or more answers as necessary.

Consent was implied by voluntary participation and no financial incentive or reward was given for completing the survey. The survey was approved by the Research Ethics Committee of the Osaka Women's and Children's Hospital

Results

In Japan, 213 PMCs possessed iNO equipment, of which 111 PMCs were Level II and 102 PMCs were Level III.

Level III is a perinatal center designated by the organization by national government and functioning as a center facility at each prefecture, while level II is a perinatal center certificated only by prefectural government and has cooperative roles with a level III center.

A total of 143 [64 Level II, 57.7% (64/111); 79 Level III, 77.5% (79/102)] PMCs provided responses, representing a response rate of 67.1% (143/213) (Table 1).

In these 143 PMCs, 2,364 extremely preterm infants are cared in a year (2013 or 2014) that is about 90% of extremely preterm infants in Japan.

Preterm infants were treated with iNO in 141 of the 143 responding PMCs (98.6%), and most of them (127/141, 90.1%) had no limitations for use regarding gestational age (GA); i.e., iNO therapy was used at less than GA < 28 weeks.

<Diagnosis of PH>

Of the 143 PMCs that responded, 126 (88.1%) did not have different criteria for diagnosis of PH between term and preterm infants.

Diagnosis of PH was performed based on echocardiography findings in 136 PMCs (100% of valid answers), differential SpO_2 in 129 PMCs (94.9%), and oxygenation index (OI) in 70 PMCs (52.9%)(Table 2).

Echocardiography is commonly performed by a neonatologist on duty to check of PH, right ventricular pressure gradient estimated by measuring the peak velocity of tricuspid regurgitation, the presence of a right-to-left shunt in the ductus arteriosus and/or foramen ovale, or if the septum was flattened or bowed into the left ventricle at end systole.

<Use of iNO>

The first choice of treatment for PH was different between exact PH (systemic BP is moderate and stable) and relative PH (systemic BP is low and unstable). (Mean BP ≥ gestational week is moderate.)

In the case of exact PH, 103 (72.0%) PMCs chose iNO as the initial therapy. On the other hand, in the case of relative PH, iNO therapy was chosen first by only 46 (32.2%) PMCs, and some attempts (volume loading, steroid and/or catecholamine) were made to increase systemic BP (Table 3, Figure 1).

Seventy-three (51.0%) PMCs had intervention criteria of iNO therapy for extremely preterm infants based on a combination of various findings, i.e., FiO_2, % differential SpO_2, OI, and echocardiography findings (Figure 2).

Fifty of 143 PMCs (35.0%) had exclusion criteria for iNO therapy in extremely preterm infants. The most common complication and was bleeding tendency, followed by IVH (≥ III). In addition, there were some other complications, i.e., chromosomal abnormality (trisomy 18), high flow PH, *etc.*

iNO therapy could be initiated within 1 hour in 96% of PMCs during the day shift and 87% of PMCs during the night shift.

The initial concentration of iNO for extremely preterm infants was 20 ppm in 41/143 (28.7%) PMCs and ≤ 10 ppm in 71/143 (49.7%) PMCs.

In extremely preterm infants, cardiac function was routinely checked by a neonatologists using echocardiography every ~8 hours in 41 (28.7%) PMCs and every 9 – 12 hours in 50 (35.0%) PMCs. During iNO therapy, PH status and cardiac function were checked by echocardiography every ~4 hours in eight (5.6%) PMCs, every 5 – 8 hours in 76 PMCs (53.1%), and every 9 – 12 hours in 39 PMCs (27.3%)(Figure 3).

<Weaning of iNO>

According to the most frequent values, weaning of iNO treatment was started when differential SpO_2 disappeared, SPO_2 reached 100%, PaO_2 reached $>80-100$ mmHg, or OI decreased to <10.

Seventy-nine percent (113/143) of PMCs began weaning from FiO_2. First, FiO_2 is decreased from 1.0 to $0.4-0.6$, and then iNO concentration is decreased from 10 ppm to 5 ppm.

In weaning of iNO, 34.3% (49/143) of PMCs were aware of the need for weaning as soon as possible to minimize the risk of exacerbation of complications.

After iNO concentration has reached 5 ppm, the iNO concentration is decreased gradually and carefully in five steps in 47 PMCs (32.9%), three steps in 26 PMCs (18.2%), and four steps in 32 PMCs (22.4%)(Figure 4-a).

It took 12 – 24 hours to go from 5 ppm to 0 ppm in 48 PMCs (33.6%) and 24 – 48 hours in 35 PMCs (24.5%)(Figure 4-b).

Discussion

Large numbers of Japanese extremely preterm infants received iNO under a diagnosis of PPHN based on echocardiography findings in all PMCs included in the present survey. Echocardiography is also commonly used by neonatologists to screen for major anomalies and hemodynamic assessment of PH, PDA, *etc*. Cardiac function was routinely checked by a neonatologist within every 12 hours in 91 (63.6%) PMCs. During iNO therapy, PPHN status and cardiac function are further checked within every 8 hours in 84 (58.7%) PMCs. Real-time echocardiography assessment allows neonatologists to respond both rapidly and precisely, with weaning of iNO carefully and as soon as possible. This may minimize the risk of exacerbation of complications, such as patent ductus arteriosus (PDA), IVH, *etc*. This is thought to be the main reason why iNO is predominantly and safely used as an early rescue therapy for PH in extremely preterm infants in Japan. In fact, post-marketing surveillance in Japan performed in 2014 by a company offering iNO therapy indicated that the mortality rate in extremely preterm infants was not higher than those in infants born at GA < 34 weeks or in late-preterm infants born at GA 34 – 36 weeks.

It should be recognized that not all preterm infants with hypoxic respiratory failure have the same underlying hemodynamic pathology, and therefore they are unlikely to all respond to the same treatment.[15]

In addition, a treatment strategy should be planned differently by exact PH or relative PH. In the case of relative PH, an increase of systemic BP might be effective before initiation of iNO.

This study had the limitation that only data from responders to the questionnaire were analyzed. Therefore, it was very difficult to evaluate precise procedures during iNO for extremely preterm infants in different hospitals. However, the responses from many different PMCs were quite similar. Thus, most Japanese NICUs apply iNO therapy using an almost standardized method in extremely preterm infants with lower mortality rates than in older gestational age.

Based on the present survey, a standardized protocol for rescue use of iNO treatment in extremely preterm infants is proposed in Fig. 5.

- Diagnosis of exact PH and initiation of iNO treatment should preferably be based on echocardiography findings.
- Initial dose of iNO treatment for extremely preterm infants is 10 ppm.
- During iNO treatment, periodic echocardiography evaluation is recommended.
- To minimize the risk of exacerbation of complications, do not unnecessarily continue iNO therapy.

- Weaning of PH therapy is started when differential SpO_2 disappears, SPO_2 reaches 100%, PaO_2 reaches $>80-100$ mmHg, or OI decreases to <10.
- At first, FiO_2 is decreased from 1.0 to $0.4-0.6$ and then iNO concentration is decreased from 10 ppm to 5 ppm.
- iNO is decreased gradually and carefully from 5 ppm to 0 ppm in five steps over more than 12 hours.

Conclusion

This national survey in Japan indicated that, in extremely preterm infants, iNO was used as early rescue therapy for PH based on echocardiography findings performed by a neonatologist with lower mortality rates than in older gestational age. A standardized protocol for use of iNO treatment in extremely preterm infants is proposed.

However, there is insufficient evidence to evaluate a safety and further follow-up studies are needed about long-term influence and safety of iNO therapy in extremely preterm infants.

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Women's and Children's Hospital, Takatsuki General Hospital, Kansai Medical University, Hirakata Hospital, Osaka City General Hospital, Aizenbashi Hospital, Hyogo Prefectural Kobe Children's Hospital, Kobe Municipal Medical Center, Nara Medical University Hospital, Wakayama Medical University Hospital, Tottori University Hospital, Shimane Prefectural Central Hospital, Kurashiki Central Hospital, Okayama Medical Center, Hiroshima City Hospital, Hiroshima Prefectural Hospital, Shikoku Medical Center for Children and Adults, Ehime Prefectural Central Hospital, Kochi Health Sciences Center, St.Mary's Hospital, Kurume University Hospital, Kitakyushu Medical Center, University of Occupational and Environmental Health Hospital, Fukuoka University, Kyushu University Hospital, Iizuka Hospital, Saga National Hospital, Nagasaki Medical Center, Kumamoto Municipal Hospital, Kumamoto University Hospital, Oita Prefectural Hospital, Miyazaki University Hospital, Okinawa Prefectural Southern Medical Center, Okinawa Prefectural Chubu Hospital, and Himeji Red Cross Hospital.

Author contribution:

J.S. conceptualized and designed the study, created the questionnaires, carried out the initial analyses, drafted the initial manuscript.

S.K. approved this study.

J.S., S.K., K.C., A.N., T.H., H.S., S.S., M.O., S.Y. and S.W. reviewed and revised the questionnaires and the manuscript.

All authors read and approved the final manuscript.

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Table 1. Response rate of PMCs possessing iNO equipment

There were 102 Level III and 292 Level II at this study(2015).

	Number of responses	Number of PMCs possessing iNO equipment	%
Level III	79	102	77.5
Level II	64	111	57.7
total	143	213	67.1

iNO, inhaled nitric oxide; PMCs, perinatal medical centers

Table 2. Parameters used for a PH diagnosis (no responses from 7 PMCs)

Diagnosis of PH was performed based on echocardiography findings in 136 PMCs (100% of valid answers), differential SpO_2 in 129 PMCs (94.9%), and OI in 70 PMCs (52.9%).

Parameter	n (% of 136 PMCs)
Echocardiography findings	136 (100)
differential SpO_2	129 (94.9)
OI	72 (52.9)

PH, pulmonary hypertention; PMCs, perinatal medical centers; OI, oxygenation index

Table 3. First choice of therapy for PH

In the case of exact PH, 103 (72.0%) PMCs chose iNO as the initial therapy.

In the case of relative PH, iNO therapy was chosen first by only 46 (32.2%) PMCs, and some attempts (volume loading, steroid and/or catecholamine) were made to increase systemic BP by 82(57.4%) PMCs.

	exact PH:N (%)	relative PH:N (%)
iNO	103 (72.0)	46 (32.2)
volume loading	8 (5.6)	45 (31.5)
steroid	0 (0)	5 (3.5)
vasodilator	7 (4.9)	1 (0.7)
catecholamine	8 (5.6)	32 (22.4)
others	7 (4.9)	4 (2.8)
invalid	10 (7.0)	10 (7.0)

PH, pulmonary hypertention; iNO, inhaled nitric oxide; PMCs, perinatal medical centers; BP, blood pressure

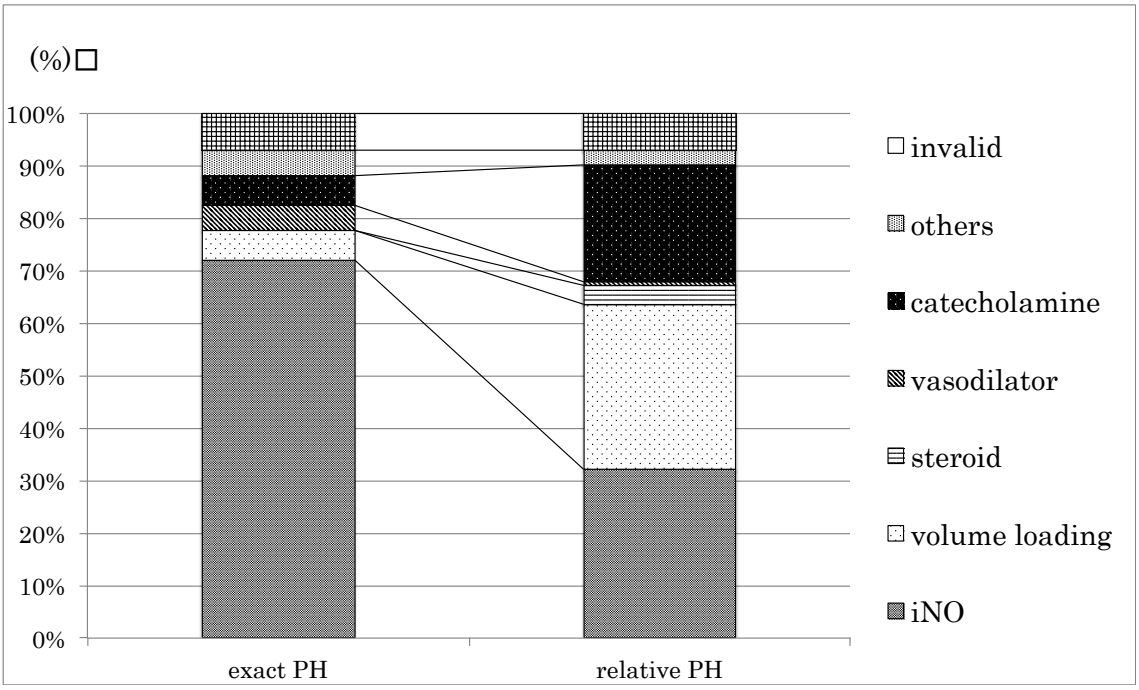
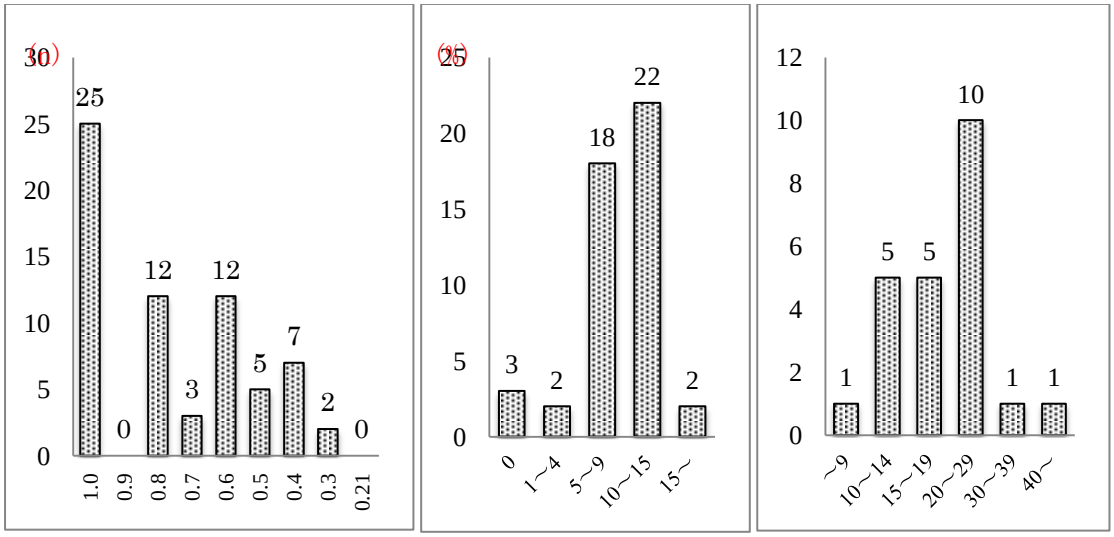


Figure 1. Differences in first choice of therapy for exact PH and relative PH

PH, pulmonary hypertention; iNO, inhaled nitric oxide



FiO_2 (%) % of differential SpO_2 OI

Figure 2. Intervention criteria for iNO therapy(at 73 PMCs)

OI, oxygenation index; iNO, inhaled nitric oxide

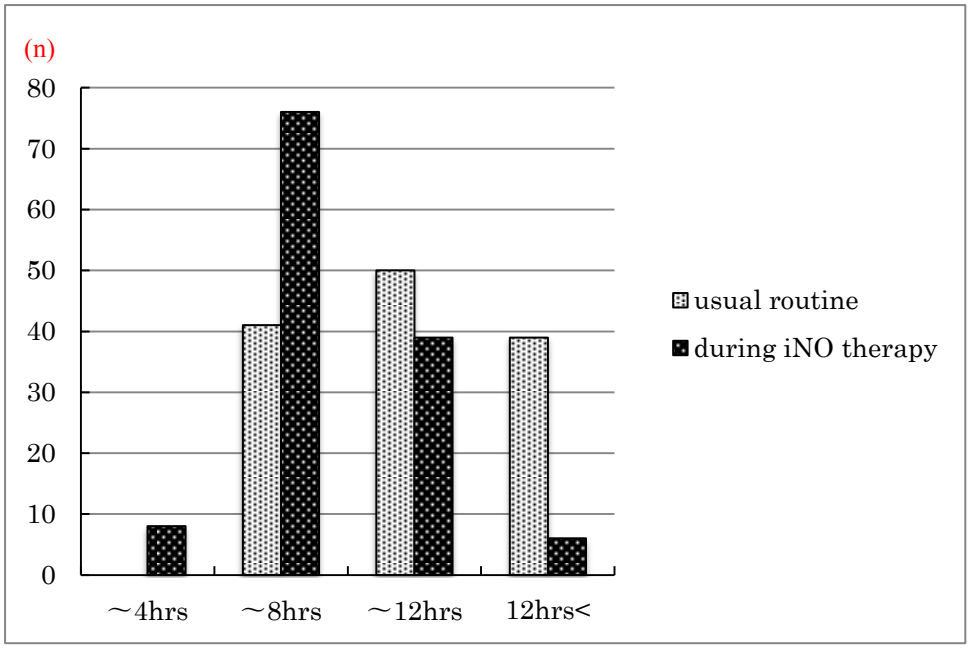


Figure 3. Frequency of echocardiogramphy

During iNO therapy, PPHN status was further checked more often by echocardiography.

iNO, inhaled nitric oxide; PPHN, persistent pulmonary hypertention of the newborn

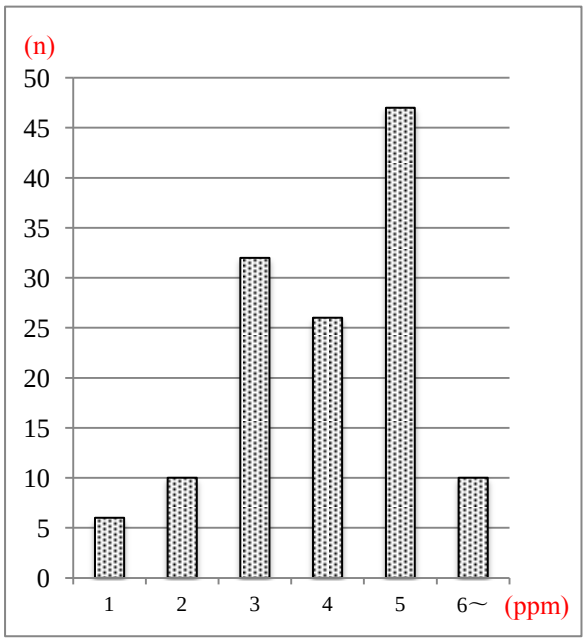


Figure 4-a. Steps from 5 ppm to 0 ppm

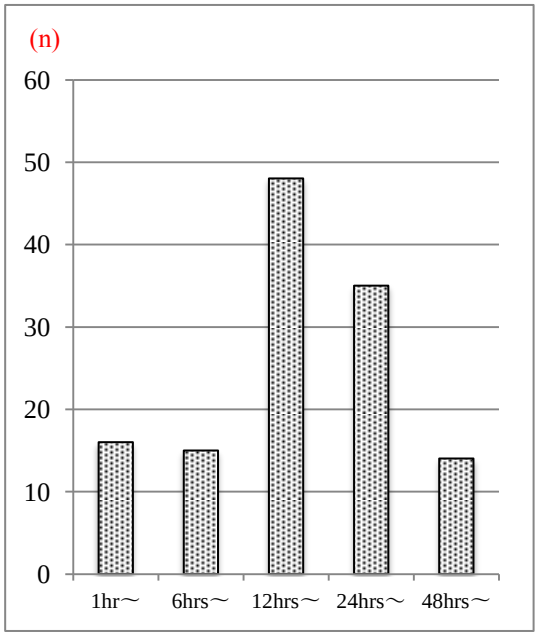


Figure 4-b. Hours from 5 ppm to 0 ppm

After iNO concentration has reached 5 ppm, the iNO concentration is weaned gradually in many steps and carefully for long hours.

iNO, inhaled nitric oxide

- Initiation
- Weaning of FiO2
- Weaning of iNO
- Weaning of iNO from 5ppm to 0ppm for more than 12hrs

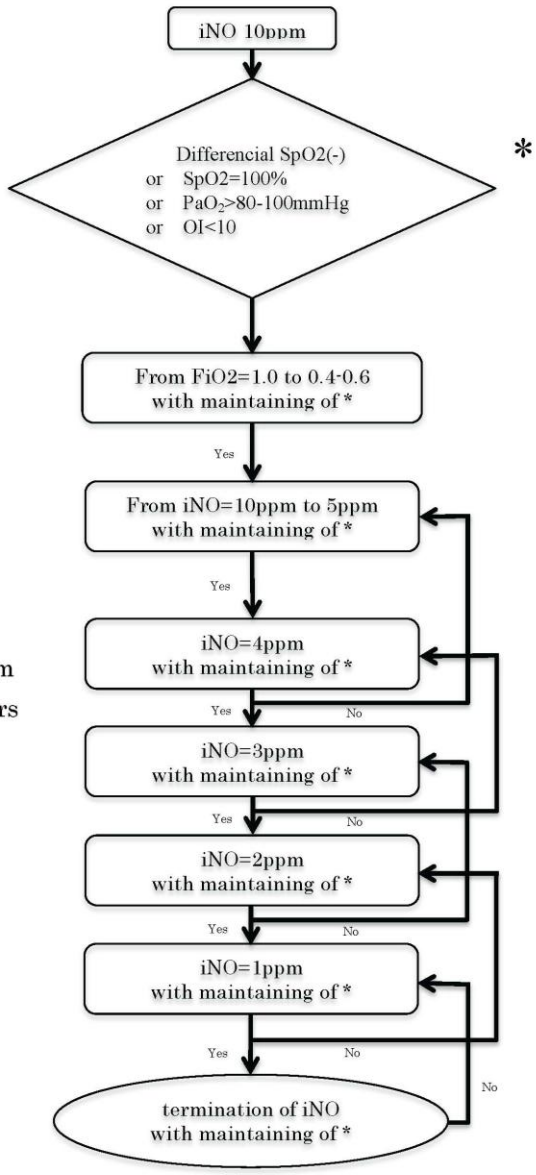


Figure 5. Schema of iNO treatment for extremely preterm infants
iNO, inhaled nitric oxide; OI, oxgenation index