

Use of inhaled nitric oxide in pediatric cardiac intensive care unit

Pediatric kardiyak yoğun bakım ünitesinde inhale nitrik oksit kullanımı

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ABSTRACT

Objective: Experience with administration of inhaled nitric oxide (iNO) in pediatric cardiac intensive care unit was retrospectively reviewed.

Methods: Data from 32 pediatric patients treated with iNO between 2011 and 2012 were collected. Patients were divided into 3 groups: Group I comprised postoperative patients, Group II comprised newborns with persistent pulmonary hypertension (PPH), and Group III comprised patients with primary pulmonary hypertension (PH) or Eisenmenger's syndrome. Age, sex, weight, primary diagnosis, arterial blood sample, pulmonary artery pressure (PAP), systemic arterial pressure (SAP), and oxygen saturation levels were analyzed.

Results: Groups I, II, and III included 25, 3, and 4 patients, respectively. Median weight was 8 kg (range: 3–40 kg), and median age was 7 months (range: 2 days–10 years). On average, iNO treatment was initiated at the 12th hour after admission to the unit (range: 1–48 hours) and continued for a median duration of 24 hours (range: 12–168 hours). Systolic PAP was 40±15 mmHg, mean SAP was 57±18 mmHg, PAP/SAP ratio was 0.69, and oxygen saturation levels were 88% prior to iNO treatment. Following iNO treatment, PAP decreased to 24±9 mmHg ($p<0.05$), PAP/SAP ratio decreased to 0.4 ($p<0.05$), SAP showed no change (60±12 mmHg), and saturation levels increased to 98% ($p<0.05$). Seven patients died during follow-up (Group I, n=5; Group II, n=1; Group III, n=1).

Conclusion: iNO seems to effectively reduce PAP, and can be used effectively and safely to prevent pulmonary hypertensive crises in pediatric cardiac intensive care units.

ÖZET

Amaç: Bu çalışmada pediatrik kardiyoloji yoğun bakım ünitesi'nde tedavi amaçlı inhale nitrik oksit (iNO) kullanılan olgular değerlendirildi.

Yöntemler: 2011–2012 yılları arasında pediatrik kardiyoloji yoğun bakım ünitesinde iNO kullanılan 32 olgu çalışmaya alındı. Hastalar üç gruba ayrıldı. Grup I (ameliyat sonrası hastalar), Grup II (direkten pulmoner hipertansiyonlu yenidoğan hastalar), Grup III (primer hipertansiyon veya Eisenmenger Sendrom'lu hastalar). Yaş, cinsiyet, ağırlık, primer tanı, kan örneği, pulmoner arter basıncı (PAB), sistemik arteriyel basınç (SAB), oksijen satürasyonu değerleri incelendi.

Bulgular: Grup I'de 25 olgu, Grup II'de 3 olgu, Grup III'te 4 olgu mevcuttu. Olguların ortalama yaşı 7 ay (dağılım, 2 gün–10 yaş) ve ortalama ağırlığı 8 kg (dağılım, 3–40 kg) idi. iNO ortanca başlama zamanı 12 saat (dağılım, 1–48 saat) ve ortanca kullanım süresi 24 saat (dağılım, 12–168 saat) idi. iNO öncesi ortalama sistolik PAB 40±15 mmHg, ortalama SAB 57±18 mmHg, PAB/SAB=0.69, oksijen satürasyonu %88 idi. Olguların iNO sonrası PAB 24±9 mmHg, SAB 60±12 mmHg, PAB/SAB=0.40, oksijen satürasyonu %98 idi. Pulmoner arter basıncı ve PAB/SAB oranı anlamlı olarak düşerken, satürasyonda yükselme saptandı ($p<0.05$). Yedi hasta takip sırasında kaybedildi (Grup I, n=5; Grup II, n=1; Grup III, n=1).

Sonuç: İNO etkin bir şekilde pulmoner arter basıncını azaltmaktadır. Pediatrik kardiyoloji yoğun bakım ünitesinde iNO'nun etkin kullanımının pulmoner hipertansif krizin yönetiminde mortalite ve morbidite üzerinde olumlu etkisi olmaktadır.

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Pulmonary hypertension (PH) is rare in childhood, though it is one of the most prominent causes of mortality and morbidity in cases of congenital heart disease. PH is generally defined as a resting mean pulmonary artery pressure (PAP) of >25 mmHg, a pulmonary wedge pressure of <15 mmHg and a pulmonary vascular resistance (PVR) of >3 Wood units.^[1,2] This definition, however, is more accurately applied in adult patients. In pediatric patients, PH may be more generally defined as systolic PAP measuring more than half systemic blood pressure. Clinically, these patients show increased vasoreactivity, particularly in stressful situations, and increased PVR, which causes acute right heart failure, circulatory collapse, and fatal pulmonary hypertensive crisis.^[1,2]

Inhaled nitric oxide (iNO), a potent and selective pulmonary vasodilator with no systemic vasodilatory effect, is often a preferred agent in the treatment of PH in intensive care units. It has antithrombotic and antiproliferative effects, and increases cyclic guanosine monophosphate concentration by diffusing into pulmonary vascular smooth muscle cells, enabling calcium reuptake into the sarcoplasmic reticulum, resulting in muscle relaxation. iNO increases oxygenation by decreasing PAP and PVR. Moreover, it deactivates rapidly via combination with hemoglobin, causing minimal systemic effects.^[2,3]

It has been suggested that iNO be used at 20–40 ppm in the ventilator circuit. Compared with other vasodilators, it has 2 major advantages, causing neither hypotension nor increased intrapulmonary shunting.^[4,5]

A retrospective review of experience with iNO administration in the pediatric cardiac intensive care unit of a tertiary care center is presented.

METHODS

Data was collected from 32 patients treated with iNO between 2011 and 2012 in the pediatric cardiac intensive care unit. An oxygen index (OI) greater than 25 was considered the criterion for initiation of iNO therapy. OI was calculated by multiplying the percentage of inspired oxygen (FiO₂) by mean airway pressure, then dividing the product by PaO₂ (OI = [FiO₂ x mean airway pressure] / PaO₂).^[6]

Demographic data including age, weight, gender, and progress of primary underlying disease were re-

corded, and information was obtained regarding iNO administration, including primary indication (hypoxemic respiratory failure, PH, etc.), specific PH therapy instituted prior to iNO, site of administration, iNO concentra-

Abbreviations:

ECMO	Extracorporeal membrane oxygenation
iNO	Inhaled nitric oxide
FiO ₂	Inspired oxygen
metHb	Methemoglobin
NO	Nitric oxide
OI	Oxygen index
PAP	Pulmonary artery pressure
PH	Pulmonary hypertension
PPH	Persistent pulmonary hypertension
PVR	Pulmonary vascular resistance
SAP	Systemic arterial pressure
TA	Truncus arteriosus

tion at initiation, and highest concentration used. Patients were divided into 3 groups; Group I comprised patients with postoperative PH, Group II comprised newborns with persistent pulmonary hypertension (PPH), and Group III comprised patients with primary PH or Eisenmenger's syndrome.

INO (Westfalen AG, Steinhagen, Germany) was administered at a dose of 20 ppm using a commercially available Dräger Nodomo system of nitric oxide (NO) application and concentration measurement (Dräger, Lübeck, Germany). Depending on patient requirement, the highest value reached was 40 ppm. Vanderbilt Children's Hospital iNO weaning protocol was used.^[7] Efforts to wean patients from iNO aim to achieve the lowest therapeutic dose, with oxygenation or mean arterial pressure as outcomes. Further attempts at weaning are made every 12 hours until iNO can be discontinued safely. According to this protocol, planned extubation follows achievement of hemodynamic stability (6 hours without pulmonary hypertensive crisis, urine output >0.5 mL/kg/hr, lack of acidosis, systemic arterial pressure [SAP] within normal limits), and normal blood gas values (FiO₂ <40%, aided respiratory rate planned according to age, PCO₂ <45 mmHg).

Arterial blood gases, PAP, SAP, and pulse oximetry levels were analyzed. In postoperative patients, iNO therapy was supplemented with 0.5 µg/kg/min of milrinone, 0.1 mg/kg/hr of cisatracurium for muscle relaxation, 0.075–0.15 µg/kg/min of fentanyl, and 0.1 mg/kg/hr of midazolam for sedation. Controlled hyperventilation was instituted to attain arterial blood pH values >7.45 and PCO₂ levels <40 mmHg. No other vasodilator was administered. Invasive SAP and PAP were measured every hour during iNO treatment.

Before and after iNO treatment, PH was confirmed by Doppler echocardiography using modified

Bernoulli equation, measuring the peak velocity of tricuspid regurgitation (as $p=4v^2$, in which p is peak pressure drop from the right ventricle to the right atrium, and v is peak velocity of tricuspid regurgitation [m/s]), which has been shown to correlate with invasive transcatheter measurements or pulmonary artery catheter at baseline.^[5-7] Invasive pulmonary artery catheter and echocardiography were used in 21 patients, while echocardiography alone was used in 11.

Statistical analysis

Statistical analyses were performed with SPSS software (version 11.5; SPSS Inc., Chicago, IL, USA). Data are expressed as mean±SD if normally distributed, or as median (range). One-way analysis of variance was used to compare mean values among groups. Wilcoxon test was performed to assess dependent repetitive measurements. A p value of <0.05 was considered statistically significant.

RESULTS

Groups I, II, and III included 25, 3, and 4 patients, respectively. Eighteen patients were male. Median

weight was 8 kg (range: 3–40 kg), and median age was 7 months (range: 2 days–10 years). iNO treatment was initiated at the median 12th hour (range: 1–48 hours) after admission to the unit and was continued for a median duration of 24 hours (range: 12–168 hours). Three patients received iNO under extracorporeal membrane oxygenation (ECMO) (Group I: $n=2$; Group II: $n=1$).

Diagnoses of Group I patients were atrioventricular septal defect ($n=9$), total anomalous pulmonary venous connection ($n=5$), ventricular septal defect ($n=3$), truncus arteriosus (TA) ($n=3$), tetralogy of Fallot ($n=2$), hypoplastic left heart syndrome ($n=2$), and patent ductus arteriosus ($n=1$). Demographic characteristics are shown in Table 1.

Prior to iNO treatment, mean systolic PAP was 40 ± 15 mmHg, mean SAP was 57 ± 18 mmHg, PAP/SAP ratio was 0.69, and oxygen saturation levels were 88%. Following iNO treatment, PAP decreased to 24 ± 9 mmHg ($p=0.001$), PAP/SAP ratio decreased to 0.4 ($p=0.001$), SAP did not change (60 ± 12 mmHg; $p=0.125$), and saturation levels increased to 98% ($p=0.001$). Statistical results are shown in Table 2.

Table 1. Demographic characteristics

Sex (n)	
Male	18
Female	14
Age, day, median (range)	210 (2–3650)
Weight, kg, median (range)	8 (3–40)
Saturation, percentage, median (range)	82 (68–95)
Beginning of nitric oxide inhalation, hour, median (range)	12 (1–48)
Nitric oxide dosage, ppm, median (range)	20 (10–40)
Group (n)	
I (Congenital heart disease)	25
Atrioventricular septal defect	9
Total anomalous pulmonary venous connection	5
Ventricular septal defect	3
Truncus arteriosus	3
Tetralogy of Fallot	2
Hypoplastic left heart syndrome	2
Patent ductus arteriosus	1
II (Newborns with persistent pulmonary hypertension)	3
III (Primary pulmonary hypertension or Eisenmenger)	4
Total	32

Table 2. Statistical results of nitric oxide usage

		Group I	Group II	Group III	Total	<i>p</i> *
		Mean±SD	Mean±SD	Mean±SD	Mean±SD	
PAP	Before nitric oxide	41±12	34±3	43±17	40±15	0.614
	After nitric oxide	24±8	21±2	32±9	24±9	0.128
	<i>p</i> **	0.001	0.050	0.070	0.125	
SAP	Before nitric oxide	58±17	50±14	57±17	57±18	0.766
	After nitric oxide	60±12	56±3	60±9	60±12	0.880
	<i>p</i> **	0.217	0.285	0.713	0.001	
PAP/SAP	Before nitric oxide	0.71±0.1	0.70±0.1	0.69±0.1	0.69±0.1	0.830
	After nitric oxide	0.41±0.1	0.35±0.1	0.47±0.1	0.40±0.2	0.460
	<i>p</i> **	0.001	0.050	0.080	0.001	
Saturation (SaO ₂)	Before nitric oxide	87±8	90±3	85±3	88±7	0.733
	After nitric oxide	97±3	99±1	89±3	98±4	0.001
	<i>p</i> **	0.001	0.100	0.070	0.001	

*Between 3 groups; **Each group. PAP: Mean systolic pulmonary arterial pressure; SAP: Mean systemic arterial pressure; SD: Standard deviation.

Five Group I patients died in the early postoperative period; 2 had complete atrioventricular septal defect, 1 had TA, and 2 had hypoplastic left heart syndrome. One patient with complete atrioventricular septal defect and 1 with TA died from persistent pulmonary hypertensive crisis. The other 3 died from sepsis and multiorgan failure in the period following iNO therapy.

One Group II patient died. This patient had been born with meconium aspiration and had undergone cardiopulmonary resuscitation at another hospital. Echocardiography was compatible with PPH. While PAP had decreased following iNO therapy, the patient died from *Klebsiella pneumoniae* septicemia 10 days after iNO cessation.

A 1-year-old Group III patient died. While echocardiography showed no structural pathology, right ventricular pressure was suprasystemic (100 + 10 mmHg; systolic arterial pressure: 80/60 mmHg). The patient underwent cardiac catheterization with iNO support, and pulmonary hypertensive crisis and cardiac arrest occurred, after which ECMO support was initiated. Suprasystemic PAP persisted, and the patient died from multiorgan failure.

Treatment of 12 Group I patients was switched to oral sildenafil, initiated at 2 mg/kg/day, divided into 4 doses. Methemoglobin (metHb) levels were 0.3–6.4%,

and were >2.5% in 3 patients. No patient required therapy for elevated metHb. One patient had elevated carboxyhemoglobin (maximum 5.5%), which did not require treatment. Thrombocytopenia developed in 2 patients. One had hypoplastic left heart syndrome, the other had PPH. Thrombocytopenia improved a few days after cessation of iNO.

DISCUSSION

In the present retrospective review, patients were divided into 3 groups; Group I comprised patients with postoperative PH, Group II comprised newborns with PPH, and Group III comprised patients with primary PH or Eisenmenger's syndrome.

Results pertaining to Group I will be discussed first. Acute PH episodes can occur due to acquired or congenital cardiac disease following open heart surgery and are believed to be a consequence of cardiopulmonary bypass, which results in pulmonary vascular endothelial tissue dysfunction and decreased endogenous NO production.^[6] Many reports have recommended iNO treatment of PH after cardiac repair in congenital heart disease cases.^[6,7] The first reported randomized clinical trial was conducted by Russell et al., and included 35 patients with specific congenital heart defects and documented preoperative PH.^[8] These patients, who were to undergo cardiopulmo-

nary bypass, were prospectively enrolled for surgical correction of their congenital heart defects, either through preoperative echocardiography or cardiac catheterization. Preoperative PH was defined as mean PAP >50% of mean SAP. Study protocol included 20-minute administration of either iNO at 80 ppm or a placebo, nitrogen, combined with 90% FiO₂ and adequate ventilation. Thirteen patients had documented postoperative PH. Of this group, 8 received placebo gas, and in the remaining 5 who received iNO, the response was fairly dramatic, with rapid and sustained 20% reduction in PAP, compared to baseline values.

In a randomized, placebo-controlled, double-blind study by Miller et al., use of iNO was associated with fewer pulmonary hypertensive crises, shorter times to extubation, and shorter duration of gas usage.^[9] In one of the largest investigations of iNO in postoperative pediatric cardiac surgery (n=124), Day et al. demonstrated a significantly lower PVR index (p<0.001) in the iNO group than in the placebo group.^[10] An iNO concentration of 20 ppm was used to treat 20 patients; however, the beneficial effects on pulmonary hemodynamics after correction of congenital heart disease were never demonstrated. Moreover, a recent retrospective study by Journois et al. examined mortality in 64 patients and showed a significant decrease in patients receiving iNO (24%), compared with a control group receiving conventional care (56%; p=0.02).^[11] However, limitations of iNO therapy for those with postoperative PH include incomplete elimination of pulmonary hypertensive crisis and the possibility of fatal rebound PH after iNO discontinuation.^[12]

In the present study, 25 patients received iNO treatment of PH in the postoperative period. As in other studies, PAP decreased significantly. Two patients did not respond to therapy and died from pulmonary hypertensive crisis.

Regarding Group II, PPH, which has high morbidity and mortality due to difficulties with treatment, is significant when encountered in newborns. A wide range of vasodilator drugs have been used in treatment, as the primary pathogenetic event is pulmonary vasoconstriction. Improved prognosis has been reported with iNO and ECMO therapies administered in well-equipped, experienced newborn centers.^[13]

A prospective, multicenter, randomized, controlled, double-blind study carried out by the Neo-

natal Inhaled Nitric Oxide Study Group concluded that PPH patients treated with iNO had less need for ECMO than those in the control group.^[14] Though no control group was included, PAP decreased with iNO therapy in 3 PPH patients adopted from other centers due to possible need for ECMO, and ECMO was not needed.

Finally, issues and results pertaining to Group III will be examined. In the lungs, reflex constriction of the pulmonary vasculature diverts blood flow to better-ventilated areas in a process known as hypoxic pulmonary vasoconstriction. Intrapulmonary shunting increases with the use of systemic vasodilators due to increased blood flow in both well- and low-ventilated regions, as a result of hypoxic pulmonary vasoconstriction inhibition. In contrast, iNO vasodilates selectively, only affecting regions that are adequately ventilated. This improves the ventilation-perfusion mismatch, improving oxygenation. Reversal of the rise in PVR from hypercarbia has also been described, suggesting a secondary benefit of iNO in patients with hypoxic respiratory failure, on whom the technique of permissive hypercapnia is commonly employed.^[15]

Budts et al. treated primary PH and Eisenmenger's syndrome in 21 patients with iNO.^[15] Pulmonary vasodilatation in response to iNO was observed in 29% of patients and was influenced by baseline pulmonary hemodynamics.

Pulmonary vasoreactivity test is recommended to demonstrate the effectiveness of calcium-channel blockers and the contribution of reversible vasoreactivity to the clinical status of patients with idiopathic PH. Although no established consensus exists regarding the agent, iNO, iloprost, adenosine, and epoprostenol are used in the pulmonary vasoreactivity test of vasodilatory response. A longer survey (5-year survey around 95%) was reported in PH patients with positive acute vasodilatory answer in PVT.^[16,17] Another study reported the long-term survey as unchanged where positive vasoreactivity was provided by iNO.^[18]

Four Group III patients received iNO treatment in the present study. Pulmonary vasodilatation in response to iNO was observed in 50% of patients.

iNO has been proven to be generally safe, with few adverse effects. As with most other therapeutics, risk of toxicity increases with concentration. Major risks

are caused by increased levels of metHb and carboxyhemoglobin.

Normal metHb levels are <1%. Causes of elevated metHb in the blood may be genetic, dietary, idiopathic, or due to chemical agents. The administration of iNO in the intensive care unit should be managed with close monitoring of metHb for the duration of therapy, particularly in patients breathing 80 ppm or more of nitric oxide.

In a case in which iNO led to increased levels of metHb, Syed et al. described a patient with Down syndrome who had undergone total correction of complete atrioventricular septal defect at the age of 5 months.^[19] iNO was used in the intensive care unit to treat pulmonary hypertensive crisis. However, metHb increased to 72% on the first day of treatment. Methylene blue treatment was unsuccessful, and metHb decreased to 0.3% after partial plasma exchange.

In the present study, 3 patients developed temporary methemoglobinemia, with metHb levels of 3.0%–6.4%. Each had received up to 40 ppm of iNO. MetHb levels were controlled and decreased to normal with discontinuation of iNO therapy. iNO therapy was reinitiated when metHb levels normalized and was stopped once PAP was under control.

Regarding increased levels of carboxyhemoglobin, carbon monoxide is at times produced endogenously by heme oxygenases, which are expressed during stressful conditions, but which can also be induced by NO. Carbon monoxide can then bind to hemoglobin with a greater affinity than oxygen, creating COHb. This can have deleterious effects by decreasing the blood's oxygen-carrying capacity, thereby negating the potential benefits of NO. In the present study, elevated COHb was observed in 1 patient, who did not require therapy.

One side effect of iNO relates to thrombocyte functions. iNO has been reported to decrease in vivo activation and number of thrombocytes in circulation.^[20,21] In the present study, treatment of 2 newborns was stopped due to development of thrombocytopenia (<50,000/mm³) after iNO initiation.

Rebound effects often occur with the weaning of NO. It has been proposed that this is likely due to the down-regulation of endogenously produced NO through a negative feedback inhibition of NO syn-

these. However, the mechanism is not fully understood. Rebound effects can be minimized or eliminated by the implementation of a weaning schedule or use of sildenafil. In the clinic, the practice of decreasing NO was switched to use of sildenafil due to gained experience with minimizing NO rebound effects. Sildenafil was used in 12 patients (all in Group I), with successful prevention of rebound effects.

Study limitations

Limitations included relatively small number of patients, no control group, and retrospective design. It is unclear whether results were directly associated with iNO, as external factors could have influenced post-operative outcomes. An additional limitation was the absence of invasive pulmonary arterial monitoring in some patients.

Conclusion

iNO seems to effectively reduce PAP, and can be used effectively and safely to treat pulmonary hypertensive crisis in pediatric cardiac intensive care units. Clinicians should be aware of the risks of methemoglobinemia and thrombocytopenia.

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