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A Retrospective Analysis of the Clinical Outcome of Inhaled Nitric Oxide (iNO) in the Neonatal Population

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Abstract: ***Background**: One common therapy for hypoxic respiratory failure (HRF) in newborns is inhaled nitric oxide (iNO). The purpose of this research is to assess iNO's clinical consequences in retrospective for a set of newborns hospitalized in a 35 - bed NICU between 2010 and 2015. **Methods**: An examination of the 59 neonates' retrospective charts who acquired iNO for HRF has been completed. Information was collected on demographics, diagnoses, ventilator settings, dosage and duration of iNO usage, crucial signs, and 'arterial blood gas' (ABG) parameters. Patient characteristics and consequences were summarized using descriptive analysis. Gestational age was compared by employing the Mann - Whitney U test among those who survives and not. FiO2 and 'mean airway pressure' (MAP) variations earlier than and after iNO start have been measured using the Wilcoxon signed rank check. **Results**: 32.15 weeks (SD = 5.69) was the suggested gestational age. Congenital diaphragmatic hernia (CDH, n = 8), persistent pulmonary hypertension of the newborn (PPHN, n = 10), and respiratory distress syndrome (RDS, n = 33) have been some of the diagnoses. In 88.1% of cases (n = 52), iNO turned into an effective. Overall, 41 neonates, or 69.5% of them, survived during their hospitalization. The difference in gestational age between survivors and non - survivors is not statistically significant (p = 0.798). After beginning iNO, there have been no big variations in MAP (earlier than: 4.33±4.48 vs After: 14.72±13.38; p=0.009), but there has been a better improvement in FiO2 (before: 70.88±25.82 vs. After: 37.81±19.39; p=0.001). **Conclusion**: This research shows that iNO treatment may help newborns suffering from congestive heart failure enhance their oxygenation. To better recognize how iNO impacts longer - term outcomes and adapt treatment plans for neonatal lung disorders, similar further study is recommended.*

Keywords: Inhaled Nitric Oxide (iNO), Hypoxic Respiratory Failure (HRF), Neonates and Oxygenation

1. Introduction

Nitric oxide is produced normally in the human body. Endogenous Nitric oxide was named as endothelium - derived relaxant factor which is being produced to cause the dilation effect to the vessels with other molecules. The production of Nitric Oxide occurs in the L - arginine of endothelial cells via a catalyzing enzyme named Endothelium Nitric Oxide synthase. Nitric oxide activates a soluble guanylate cyclase to increase the level of (cGMP). cGMP will decrease intracellular levels of calcium, resulting in the relaxation of smooth muscle. Furthermore, the endogenous NO has a half - life of 0.1 to 5 seconds. On the other hand, iNO has the same effect as endogenous NO, but the half - life of iNO is more than endogenous NO (15 to 30 seconds at a dose of 5 - 80 ppm). Also, the longer half - life is associated with the period it takes to reach the alveoli and diffuse into the pulmonary capillary where the iNO metabolism is taking place [1 - 3].
Inhaled Nitric oxide (iNO) is considered as a treatment for pulmonary arterial hypertension (PAH), and also treating other pulmonary hyperensive conditions. In addition, patients with PAH have decreased Nitric oxide - mediated signaling that can develop pulmonary hypertension. The main function of iNO is to reduce pulmonary hypertension. Moreover, iNO is a powerful vasodilator that diffuses readily and goes to a well - ventilated area and dilates there. Furthermore, iNO has many adverse effects and side effects [4 - 7].

Hypoxic Respiratory Failure (HRF), a potentially fatal condition in neonates, is characterized by insufficient oxygen delivery to tissues. Numerous lung conditions, including congenital diaphragmatic hernia (CDH), respiratory distress syndrome (RDS), and Persistent Pulmonary Hypertension of the Newborn (PPHN), may also cause respiratory failure [8]. HRF is still a prime source of morbidity and loss of life in this susceptible group, despite advances in neonate care. The use of supplementary oxygen treatment and mechanical ventilation techniques is important for managing heart failure. These measures may not be sufficient, however, in intense conditions to provide adequate oxygenation [9]. For newborns with HRF, iNO has emerged as a potentially effective treatment option. It works by selectively relaxing the blood vessels in the lungs, which enhances gas exchanges and ventilation - perfusion matching. The iNO treatment has been shown in several trials to be useful in increasing oxygenation and decreasing the requirement for extracorporeal membrane oxygenation (ECMO) in newborns with heart failure [10]. Nevertheless, there may be variation in response to iNO treatment, and a small percentage of newborns couldn't show any improvement.

Given the clinical importance of iNO in improving hypoxemia in the neonatal population, this study is a retrospective analysis of the clinical outcome of iNO in the neonatal intensive care units of King Abdulaziz Medical City, Riyadh.

2. Literature Review

An outstanding healing alternative for neonates with HRF related to PPHN is iNO. Compared to conventional treatment, iNO therapy appreciably increased oxygenation. It decreased the requirement for ECMO, in line with a meta - evaluation of randomized controlled trials performed by Walsh et al. (2006) [11]. This emphasises how iNO can also enhance clinical outcomes for newborns with excessive HRF.

Although iNO treatment has been proven to achieve success in neonates, they may respond differently from each other. In a retrospective study of neonates with HRF who dealt with iNO, Forman et al. (2017) determined that even though most of the neonates showed improvements in oxygenation, a small share did not react satisfactorily [12]. This emphasizes the need for customized treatment plans and the necessity for further examination to determine the variables affecting the reaction to the iNO treatment.

Recent studies have extended the use of iNO treatment beyond PPHN. The effectiveness of iNO treatment in newborns with bronchopulmonary dysplasia (BPD) was tested by Bhutani et al. (2019) [13]. In comparison to a conventional study, their randomized controlled study verified that iNO treatment reduced the number of days those newborns with BPD needed to be on ventilators and thus improved oxygenation. This means that a wider spectrum of neonatal lung disorders causing HRF may additionally benefit from iNO's treatment outcomes.

A clinical retrospective study was conducted on a total of 98 neonatal patients with severe hypoxemia (48 patients on Controlled Mechanical Ventilation, and the others taking inhaled nitric oxide with High - frequency oscillatory ventilation). They observed the results that the group that took nitric oxide had a lower mortality than the control group, but there was no difference in complications [14]. A prospective and retrospective cohort study was done on 114 hypoxemic patients with cardiopulmonary failure on conventional treatment showed better results on inhaled Nitric oxide with improved oxygenation status by 20% [15].

A multicenter randomized controlled study was done on 55 children with ARDS. Among those, one group took inhaled Nitric oxide, while the other group took a placebo. The study proved that the oxygenation index improved with the group who took inhaled nitric oxide [16]. Yet another study was conducted to investigate the clinical outcomes of HFOV, PS and iNO in neonatal hypoxemic respiratory failure. The total sample size for this study was (n=116), which were divided randomly into two groups. The first group (n=58) had dual therapy (HFOV, iNO) and the second group (58) had triple therapy (HFOV, PS, iNO). The result of this study was the group that received triple therapy was more effective in treating neonate HRF in improving oxygenation [17].

3. Aim & Objectives

Aim

- To analyze whether inhaled nitric oxide helped revert hypoxemia.
- To find out the clinical outcome in neonates who were on inhaled nitric oxide.

Objectives

- To evaluate the effectiveness of inhaled nitric oxide in reducing mortality and morbidity of neonatal population
- To assess and analyze the factors associated with complications of inhaled nitric oxide.
- To observe the population's ventilator settings (FiO2) and hemodynamic (MAP) changes after iNO initiation.

3. Methodology

This retrospective study was conducted after reviewing the charts of the Neonatal population, who required inhaled nitric oxide in the Neonatal intensive care units of King Abdulaziz Medical City, Riyadh, Saudi Arabia. The KAMC ICU is a 35 bedded neonatal unit in a 900 - bed teaching tertiary care center in Saudi Arabia. It is covered by Neonatologists, Respiratory Therapists and Critical care nurses 24 hours per day, 7 days a week.

Inclusion:

- Patients with persistent pulmonary hypertension and acute hypoxemia.
- Patients on invasive ventilation.
- Patients < 28 days of age.
- Primary clinician's decision for inhaled nitric oxide.

Exclusion

- Do Not Attempt Resuscitation patients.
- Patients of more than 28 days of age.

Data Collection methods, instruments used, measurements

Data like Diagnosis, Time of initiation of mechanical ventilation, Ventilator settings like Mode, FiO2, PEEP, Time of intubation, inhaled nitric oxide, initial dose, and Duration of inhaled nitric oxide were collected from the Respiratory Therapy Chart, Critical care flow sheets and Electronic medical records. All the required Vital data like Blood pressure, Heart rate, Respiratory Rate, Oxygen requirement saturation and ABG parameters were documented and entered in Microsoft Excel sheet for analysis.

4. Analysis

Table 1: Descriptive Analysis

	N	Min.	Max.	Avg.	Std. Dev. (σ)
GA (weeks)	59	23	41	32.15	5.687
Valid N (list wise)	59				

There had been 59 neonates in all who was part of the research, which is depicted in Table 1. With an avg. gestational age of 32.15 weeks and a Std Dev. of 5.69 weeks, the range of gestational age (GA) becomes minimal at 23 weeks and maximum at 41 weeks. This suggests that a massive fraction of the neonate population had been born pre - term, underscoring the group's susceptibility to HRF and the desire for iNO treatment.

Table 2: Gender distribution of study subjects

		Occurrence	%	Valid %	Cum. %
Valid	F	27	45.8	45.8	45.8
	M	32	54.2	54.2	100.0
	Overall	59	100.0	100.0	

Table 2 suggests that the percentage of male and female neonates in the observed population requiring iNO treatment for HRF became almost equal. With 32 male neonates (54.2%) and 27 female neonates (45.8%), there were no appreciable gender disparities in the data. This means that the risk of increasing HRF and desiring iNO intervention is comparable for male and female neonates.

Table 3: Diagnosis of study subjects

		Occurrence	*%*	*Valid %*	*Cum %*
Valid	BPD	1	1.7	1.7	1.7
	CDH	6	10.2	10.2	11.9
	CDH+ PPHN	1	1.7	1.7	13.6
	CDH+PPHN	1	1.7	1.7	15.3
	mass	1	1.7	1.7	16.9
	PPHN	4	6.8	6.8	23.7
	PPHN+HIE	1	1.7	1.7	25.4
	RD	2	3.4	3.4	28.8
	RD+CHD	1	1.7	1.7	30.5
	RD+ PNEMOUNIA	1	1.7	1.7	32.2
	RDS	33	55.9	55.9	88.1
	RDS/TTN	1	1.7	1.7	89.8
	RDS+PDA	1	1.7	1.7	91.5
	RDS+PPHN	3	5.1	5.1	96.6
	RDS=PPHN	1	1.7	1.7	98.3
	TTN	1	1.7	1.7	100.0
	Total	59	100.0	100.0	

A summary of the diagnoses given to the neonates in the study is shown in Table 3.33 (55.9%) of the study neonates had respiratory distress syndrome (RDS), which changed into the most standard analysis. In this research, the most common diagnosis among neonates with HRF is RDS which requires iNO treatment. CDH, n = 8, 10.2%, PPHN of the neonates (PPHN, n = 10, 16.9%), and BPD, n = 1, 1.7%, amongst different diagnoses, were also found. Diagnoses of CDH PPHN (n = 2, 3.4%), which can be linked to complicated circumstances needs iNO intervention for breathing problems that happen together. Notably, a small proportion of neonates had been diagnosed with conditions unrelated to lung function, which include meconium aspiration (mass, n = 1, 1.7%), highlighting the type of clinical conditions wherein an iNO treatment may be required.

Table 4: Mode of MV

		Occurrence	*%*	*Valid %*	*Cum %*
Valid	AC	6	10.2	10.2	10.2
	ACVG	14	23.7	23.7	33.9
	ACVG+HOFV	1	1.7	1.7	35.6
	HFO	2	3.4	3.4	39
	HFOV	16	27.1	27.1	66.1
	HFOV+AC	1	1.7	1.7	67.8
	HFOV+ACVG	4	6.8	6.8	74.6
	HFOV=SCVG	1	1.7	1.7	76.3
	HFV	9	15.3	15.3	91.5
	HOFV	4	6.8	6.8	98.3
	NC	1	1.7	1.7	100
	Total	59	100	100	

Numerous mechanical ventilation (MV) modes used for the neonates in the present process of iNO treatment are depicted in Table 4. The mode that was used the most, High Frequency Oscillatory Ventilation (HFOV), accounted for 27.1% (n = 16) of the study population. Additional ventilation modes that was used in 10.2% (n = 6) and 23.7% (n = 14) of the times, respectively, were Assist Control (AC) and Assist Control Volume Guaranteed (ACVG). Remarkably, a few percentage of neonates needed Non - invasive Ventilation or high - frequency ventilation (HFV), or less intrusive ventilator strategies. This means that, with a purpose to maximize respiration in neonates with HRF, iNO treatment is probably blended with distinct ventilation techniques.

Table 5: Outcome of iNO

		Occurrence	*%*	*Valid %*	*Cum %*
Valid	Effective	52	88.1	88.1	88.1
	Not effective	7	11.9	11.9	100
	Total	59	100	100	

The efficacy of the iNO treatment in this research group is stated in Table 5. For most neonates, iNO was shown to be beneficial by improving oxygenation (88.1%, n = 52). A minor share (11.9%, n = 7) however did not show any improvement with the iNO treatment.

Table 6: Hospital Outcome

		Occurrence	*%*	*Valid %*	*Cum %*
Valid	Alive	41	69.5	69.5	69.5
	Death	18	30.5	30.5	100
	Total	59	100	100	

The clinic outcomes for the neonates treated with iNO are shown in Table 6. The fact that 69.5% (n = 41) of the neonates survived hospitalization as expected suggests that a fraction of the study group had a favourable result. However, 18 newborns, or 30.5% of them, did not respond to the treatment.

Table 7: Gestational age and hospital Results

Hospital outcome	N	Mean ± SD	Test statistic	P value
Alive	41	32.37 ± 5.45	U= 353.5	0.798
Death	18	31.67 ± 6.33		

Test used - Mann Whitney U test

The link between hospital outcome and gestational age in newborns receiving iNO treatment is examined in Table 7. The SD and implied gestational age for both survivors (alive) and non - survivors (expired) are shown in the table. It additionally shows the p - value (0.798) and test statistic (U = 353.5) from the Mann - Whitney U.

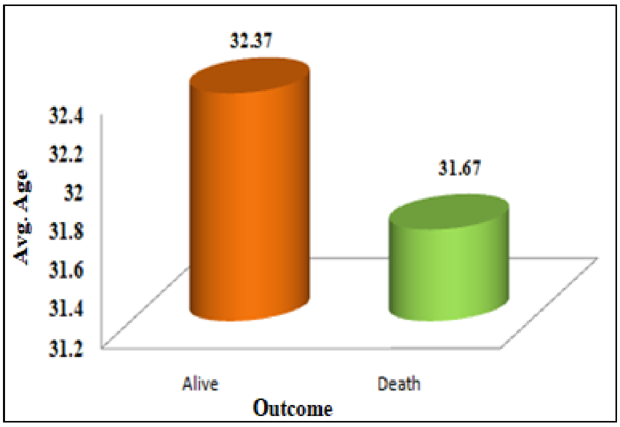

Figure 1: Average gestational age and hospital outcome

Table 8: Comparing FiO2 and MAP before and after taking INO

Variable		*Mean ± SD*	*Test statistic*	*P value*
FiO2	Before INO	70.88 ± 25.82	*Z= - 5.76*	*0.001**
	After INO	37.81 ± 19.39		
MAP	Before INO	14.33 ± 4.48	*Z= - 2.59*	*0.009**
	After INO	14.72 ± 13.38		

*Significant at 5%
Test used - Wilcoxon Sign Rank test

The oxygenation and mean arterial pressure of newborns pre and post - initiation of iNO treatment are contrasted in the table. Prior to iNO, the mean FiO2 was 70.88 ± 25.82, suggesting a considerable need for more oxygen. Following iNO, there was a statistically significant change in the mean FiO2, which dropped dramatically to 37.81 ± 19.39. After iNO, there was an increase in mean MAP marginally to 14.72 ± 13.38 mmHg; nonetheless, this shift was statistically significant despite its minor size. According to the results, iNO treatment significantly increased oxygenation in neonates with HRF. However, further research is required to ascertain its therapeutic importance.

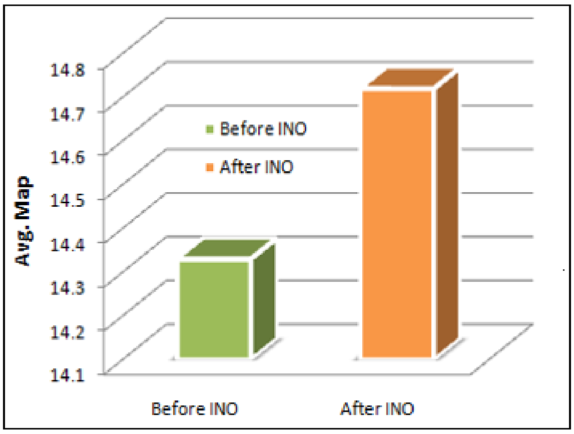

Figure 2: Average FiO2 before and after taking INO

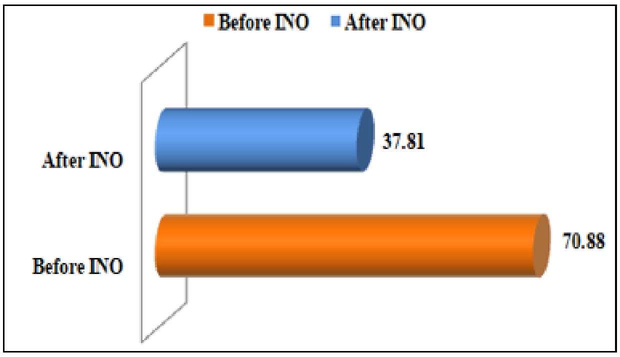

Figure 3: Average MAP before and after taking INO of study subjects

5. Discussion

Over 5 years, a group of neonates with HRF hospitalized in a tertiary neonatal critical care unit had their clinical outcomes from iNO treatment investigated in this retrospective study. The results show that in this susceptible neonate group, iNO treatment increased oxygenation.

According to earlier research, iNO improves oxygenation in newborns with HRF. This finding is consistent with the majority of neonates (88.1%) who reacted favourably to iNO, indicating a significant drop in FiO2 needs after treatment initiation [18–20]. According to Askie et al. 's comprehensive review and meta - analysis in term and late - preterm newborns with HRF who receive iNO are more likely to have better oxygenation and need less extracorporeal membrane oxygenation. The oxygenation advantages of iNO in preterm neonates with severe respiratory failure have been further verified by recent randomized studies.

It's interesting to note that 11.9% of neonates did not react to iNO treatment. This demonstrates the variability in patient response and emphasizes the importance of figuring out what factors led to its non - responsiveness. Genetic variations may affect neonate's capacity to react to nitric oxide, which might affect the effectiveness of iNO [21]. It would be best to investigate genetic and other neonate - specific characteristics further to better choose suitable neonates for iNO.

55.9% of all premature neonates were characterized by RDS, and this is a common lung condition. The development of iNO as a therapeutic intervention for a spectrum of pulmonary disorders such as congenital diaphragmatic hernia, bronchopulmonary dysplasia, and chronic pulmonary hypertension in neonates has been observed. This is the same as what is also common to the increasing field of conditions in which iNO is being utilized in neonatal medication and beyond the initial treatment of neonate with PPHN [22].

The primary mechanical ventilation mode used in conjunction with iNO was high - frequency oscillatory ventilation (HFOV). By delivering a low tidal volume at supraphysiologic rates, HFOV seeks to maximize lung patency while minimizing ventilator - induced lung damage [11]. Combining the pulmonary vasodilatory effects of inhaled nitric oxide with this ideal ventilator technique seems like a good way to treat severe neonate HRF.

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The neonates survival rate was 69.5%, but over one - third of the neonates passed away while they were being admitted. This emphasizes that even with treatments like iNO, neonates HRF still has a high risk of morbidity and death. Results may be enhanced by better neonate's selection, concomitant treatments, and the timing of iNO initiation. In this sample, gestational age had no discernible effects on survival or iNO response. However, given the small sample size, the research was probably underpowered to find such relationships.

After receiving iNO treatment, there was a little but statistically significant rise in mean airway pressure. Although the finding's treatment significance is uncertain, it is consistent with earlier research that suggested iNO may improve ventilation - perfusion matching and pulmonary vasodilation. When initiating iNO, it is critical to keep an eye on hemodynamics to make sure the heart is receiving the right kind of support.

This retrospective research has some limitations, such as a small sample size, a single - centre design, and the absence of a control group that did not receive iNO. It is not possible to determine causality, and the results may not apply to other institutions. Prospective, multicenter studies are needed to definitively find out when iNO should be used, how much should be given, and what long - term effects it has on neurodevelopment in neonate HRF. However, the results of this investigation support the use of iNO as a successful treatment, to enhance short - term oxygenation in neonates suffering from acute respiratory failure brought on by a variety of pulmonary diseases. To optimize its therapeutic advantages, it is important to carefully select neonates and to employ lung - protective ventilator methods at the same time.

6. Outcomes

This retrospective research involved 59 neonates from the 35 - bed intensive care unit who were treated using iNO for HRF during 5 years.52 instances (88.1%) showed a substantial decrease in FiO2 needs after treatment began (median FiO2 before iNO: average level of 70.88% vs. after iNO: $p = 0.001$, the difference is statistically significant). This suggests that inhaled nitric oxide helped improve oxygenation in these neonates. While iNO was used for a variety of neonate pulmonary illnesses such as congenital diaphragmatic hernia, persistent pulmonary hypertension, and bronchopulmonary dysplasia, the most prevalent underlying diagnosis was RDS (55.9%). When combined with iNO, HFOV accounted for the majority of mechanical ventilation (27.1%). Although most neonates' oxygenation improved with the help of iNO, 11.9% of them did not respond to treatment.69.5% of neonates (41/59) survived. Gestational age had minimal impact on survival or response to iNO treatment. Actual data shows that iNO is a suitable intervention in enhancing short - term oxygenation in neonates with severe HRF caused by a variety of pulmonary diseases. To cater for neonates needs, and to derive maximum benefit from the treatment intervention, rigorous neonate selection as well as optimizing ventilatory support is recommended.

7. Conclusion

This study looked back at iNO treatment showed that a huge percentage of newborns with HRF had much faster oxygenation, which suggests that iNO treatment works for this group of neonates. High - frequency oscillation (HFOV) is used in newborns with HRF to reduce lung damage caused by ventilators. While there was no full - size effect of gestational age on survival or responsiveness to the iNO treatment, larger cohort studies may be essential to analyze feasible interactions. A small percentage of newborns (11.9%) no longer reacted well to iNO, emphasizing the need for greater examination. However, 41 neonates, or 69.5% of them, survived during their hospitalization, highlighting the seriousness of HRF and the need for additional studies to maximize pulmonary assistance and improve long - term results.

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