Abstract # PA4642

A Phase III Multicenter, Randomized, Double-Blind, Controlled Trial of High-Dose Inhaled Nitric Oxide in Infants with Acute Bronchiolitis

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ABSTRACT

Background: Acute viral bronchiolitis is the most common lower respiratory infection in early infancy and a leading cause of infant hospitalization. The treatment of bronchiolitis is largely supportive. Inhaled Nitric Oxide (NO) has pulmonary vasodilatory properties and has been approved for the treatment of persistent pulmonary hypertension of the newborn. Preclinical studies show that high-dose NO possesses antibacterial and anti-viral properties[1,2]. In a recent pilot study, we have shown safety and tolerability of high-dose NO (160 ppm) in infants with moderately severe bronchiolitis[3]. **Methods**: Here, we depict data from our phase III multicenter, randomized, double-blind, controlled study comparing the efficacy of intermittent 160 ppm NO (30min, 5 times/day, up to 5 days) with standard supportive care (oxygen) in 67 infants (0-12 months, clinical score 7-10, admission to hospital) admitted to 6 hospitals across Israel. All subjects received standard of care treatment. The primary outcome measure was the Length of Hospital Stay (LOS). The secondary outcome measures were time to clinical improvement: clinical score of ≤5 (Modified Tal score[4], mTal) and SaO_2 ≥ 92% in room air. Adverse Events (AE's) and NO-related AE's including methemoglobin and Nitrogen Dioxide (NO_2) levels were closely monitored. **Results**: 67 subjects were randomized to two groups: Standard treatment group (n=34; 21 males & 13 females, mean age 16.72 ± 11.66 weeks) and NO treatment group (n=33; 20 males & 13 females, mean age 16.39 ± 11.7 weeks). Baseline characteristics, including weight at admission, gestation week, clinical score and vital signs were similar between groups. Primary endpoint LOS was reduced by 23 hours in the NO group compared to the standard treatment group (p=0.085, mean time 59.2±38.6 vs 82.2±63.2 hours, respectively). Secondary endpoint time to 92% SaO_2 was reduced by 18.2 hours in the NO group compared to the standard treatment group (mean time 42.6±28 vs 60.8±37.5 hours, respectively), and time to reach modified Tal (mTal) score of 5 was reduced by 12.1 hours in the NO group compared to the standard treatment group (mean time 39.6±24.7 vs 51.7±47.2 hours, respectively). No treatment-related SAE's were reported and MetHb and NO_2 levels remained within the accepted ranges during treatment. Vital signs including heart rate, respiratory rate, body temp and blood pressure remained comparable between groups and were not affected by treatment. **Conclusions**: Intermittent inhalations with 160 ppm NO reduces LOS, and time for clinical improvement in infants hospitalized with acute bronchiolitis. In addition, high-dose NO treatment is well tolerated and safe for these patients.

BACKGROUND

- Acute viral bronchiolitis is a common infection of the lower airways and a leading global cause of infant hospitalization resulting in enormous burden on healthcare systems.
- Treatment for bronchiolitis is largely supportive (oxygen and inhalations of hypertonic saline).
- Nitric Oxide (NO) is a natural gas molecule playing a role in various biological process including relaxation of smooth muscle cells and vasodilation of blood vessels.
- Inhaled Low-dose NO (20-80 ppm) is FDA-approved for the treatment of Persistent Pulmonary Hypertension of the Newborn (PPHN).
- High-dose NO (160 ppm) possesses antibacterial and anti-viral properties acting in multiple mechanisms involving a number of molecular targets[1,2].
- In a pilot study, high-dose NO (160 ppm) was shown to be safe and tolerable in infants with moderately severe bronchiolitis[3].
- Here we evaluate whether inhaled high-dose NO reduces hospital length of stay and time to clinical improvement in infants with acute bronchiolitis.

OBJECTIVES

Primary Endpoints

- *Length of Stay (LOS):* Assess whether 160 ppm Nitric Oxide (NO) administered intermittently via inhalation to subjects aged 0-12 months with acute bronchiolitis reduces hospital Length of Stay (LOS), compared to standard supportive treatment.

Secondary Endpoints

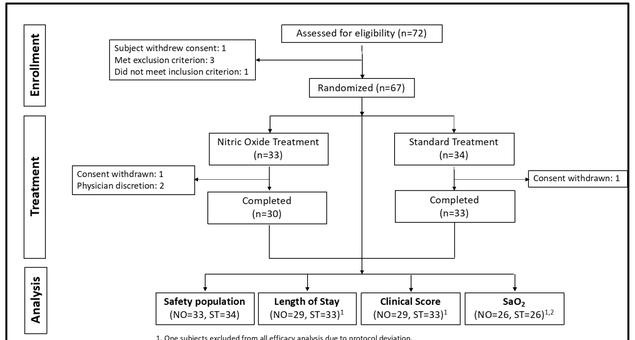
- *Time to SpO_2 ≥92%:* Assess whether 160 ppm Nitric Oxide (NO) administered intermittently via inhalation to subjects aged 0-12 months with acute bronchiolitis reduces the time required to achieve sustained 92% oxygen saturation in room air for at least 2 hours, compared to standard supportive treatment.
- *Time to Clinical score ≤5:* Assess whether 160 ppm Nitric Oxide (NO) administered intermittently via inhalation to subjects aged 0-12 months with acute bronchiolitis reduces the time required to achieve clinical improvement - a clinical score ≤5 (Modified Tal score), compared to standard supportive treatment.
- *Safety and Tolerability:* Characterize the safety and tolerability of 160 ppm NO intermittent inhalation treatment as measured by Adverse Events (AE) and Serious Adverse Events (SAE)– the number of subjects and percentage of subjects that experience each event.

METHODS

Study design

- Multi-center, double-blind, Phase 3 clinical trial comprised of a treatment period of ≥24 hours and ≤5 days with 14- and 30-day follow-up assessments.
- Subjects aged 0-12 months old with acute bronchiolitis requiring in-patient hospitalization with a clinical score of 7 to 10 at screening in room-air.
- Subjects were randomized in a 1:1 ratio to receive a combination of standard supportive treatment combined with 160 ppm NO or standard supportive treatment alone.
- Treatment schedule included five 30-minute inhalation sessions per day (24 hours). A maximum of 25 inhalation sessions per subject were administered.
- All inhalation treatments delivered by air/oxygen blender ±NO via simple mask, with a minimum FiO_2 0.21
- Delivered gas measured for NO, NO_2, O_2 concentrations with AeroNOx nitric oxide system (International Biomedical)
- SpMetHb and SpO_2 measured with commercial pulse co-oximeter (Rad-57/Rad-87, Masimo Corp.)

RESULTS



1. One subjects excluded from all efficacy analysis due to protocol deviation.
2. Time to 92% SaO_2 was performed only for subjects with <92% SaO_2 at enrollment.

***Fig. 1.* Recruitment and Randomization of Study Patients.** 67 subjects were randomized to two groups: Standard treatment: standard supportive care (oxygen). Nitric Oxide treatment: standard care plus inhaled 160 ppm NO, 30 minutes, 5 times/day for up to 5 days.

Characteristic		Std Treatment (N=34, Mean±SD)	NO + Std (N=33, Mean±SD)
Gender		21 M, 13 F	20 M, 13 F
Age (weeks)		16.72 ± 11.66	16.39 ± 11.7
Weight (Kg)		5.88 ± 1.81	5.82 ± 1.79
Gestation Week		38.17 ± 1.82	38.25 ± 1.81
mTal Clinical Score		8.49 ± 1.02	8.45 ± 1.02
Vital Signs	Temp.	37.37 ± 0.84	37.38 ± 0.85
	BP (Sys/Dia)	101.0/58.0	101.0/57.6
	Heart Rate	148.5 ± 21.33	148.37 ± 21.24
	Resp. Rate	56.85 ± 11.21	57.31 ± 11.08
	% SpO_2 (Room Air)	88.54 ± 4.04	88.69 ± 3.98

***Table 1.* Baseline Characteristics of Study Patients.** A total of 67 patients were randomized to two groups, showing a high degree of consistency between them.

RESULTS

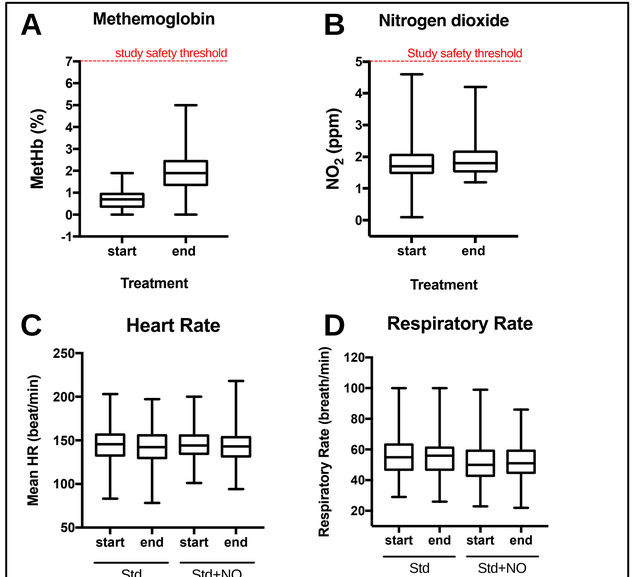


***Fig. 2.* Patient Responses to Treatments.** A) SpMetHb changes during 160ppm NO inhalations, NO treatment group, B) NO_2 exposure levels during 160ppm NO inhalations, NO treatment group, C) Heart rate at start and end of treatments, NO and Standard groups, D) Respiratory rate at start and end of treatments, NO and Standard groups.

AE's/SAE's Summary	Number			Comments
	Total	ST	NO	
Subjects with AE's	33/67	19	14	
NO-related AE's	1/14	0	1	Skin Rash. Mild. Resolved
Subjects with SAE's	11/67	5	6	
NO-related SAE's	0/6	0	0	

***Table 2.* Adverse Events Overview.**
ST: Standard Treatment
NO: Standard + Nitric Oxide Treatment

Clinical Complications	Number of Events			Comments
	Total	ST	NO	
Pneumonia	4/33	2	2	2 SAEs (1 event per group)
Fever	9/33	6	3	1 SAE (ST group). Mild
Otitis Media	4/33	4	0	1 SAE
Oxygen Desaturation	10/33	1	9	During treatment. Mild
UTI	2/33	0	2	2 SAE's. Mild and moderate
Skin Rash	2/33	0	2	1 event drug-related. Mild
Diarrhea	2/33	0	2	1 SAE
Respiratory distress	2/33	1	1	SAE
Dyspnea	1/33	1	0	SAE. Mild
Restlessness	1/33	1	0	During treatment
Bronchiolitis	2/33	0	2	2 SAE
Respiratory tract infection	1/33	0	1	SAE

***Table 3*. Adverse Events.**
*patients in NO group received slightly lower FiO_2 during NO treatment due to design.

RESULTS

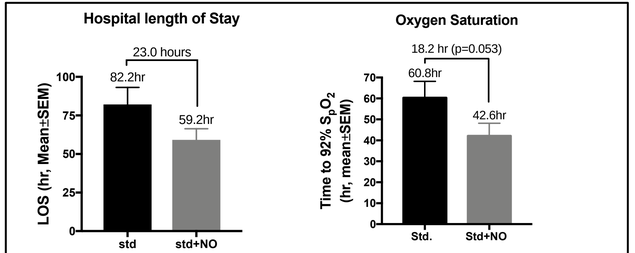


***Fig. 3.* Inhaled NO (160ppm) reduces Hospital Length of Stay (LOS) in infants with bronchiolitis.** LOS (hr) was calculated from enrollment of infant in the study to time of discharge in standard (std, n=33) and std+NO treatment (n=29) groups. Welch's t-test was performed to compare means (p = 0.085).

***Fig. 4.* Inhaled NO (160ppm) improves time to 92% oxygen saturation in infants with bronchiolitis.** Time (hr) from patient enrollment to peripheral oxygen saturation (S_pO_2) of at least 92% is shown in standard (std, n=26) and std+NO treatment (n=26) groups. Welch's t-test was performed to compare means (p = 0.053). Analysis was performed only for subjects with S_pO_2 below 92% at enrollment.

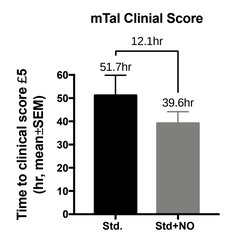


***Fig. 5.* Inhaled NO (160ppm) improves time to mTal clinical score <5 in bronchiolitis.** Time (hr) from patient enrollment to modified Tal score (mTal) score of 5 or below is shown in standard (std, n=33) and std+NO treatment (n=29) groups. Welch's t-test was performed to compare means (p = 0.20).

CONCLUSION

1. **In acute bronchiolitis patients, intermittent inhalations with 160 ppm NO resulted in clinically significant reductions in:**
   - **Length of Stay**
   - **Time to sustained 92% oxygen saturation**
   - **Time to Clinical Score improvement**
2. **The nitric oxide inhalations were well tolerated and safe for these patients.**
3. **A larger study is warranted to confirm these positive results.**

1. Fang FC. Perspective series: host/pathogen interactions. Mechanisms of nitric oxide-related antimicrobial activity. *J Clin Invest.* 1997; 99(12): 2818-2825; **2** Regev-Shoshani G, Vimalanathan S, McMullin B, Road J, Av-Gay Y, Miller C. Gaseous nitric oxide reduces influenza infectivity in vitro. *Nitric Oxide*, 2013; 31: 48-53; **3.** Tal A, Greenberg D, Av-Gay Y, Golan-Tripto I, Feinstein Y, Ben-Shimol S, Dagan R, Goldbart AD. Nitric oxide inhalations in bronchiolitis: A pilot, randomized, double-blinded, controlled trial. *Pediatric Pulmonology* 2018; 53(1): 95-10 **4.** Golan-Tripto I, Goldbart A, Akel K, dizitzer Y, Novack V, Tal A. Modified Tal Score: Validated score for prediction of bronchiolitis severity. *Pediatric Pulmonology.* 2018; 53(6): 796-801