Evaluation of Two Doses of Nitric Oxide (NO) Given Intermittently via Inhalation to Subjects with Bronchiolitis – a Multi-Center Double Blind Study

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BACKGROUND:

- Bronchiolitis is an acute inflammatory injury of the bronchioles usually caused by a viral infection with no approved treatments
- The recommended approach by the American Academy of Paediatrics is supportive care
- Nitric oxide (NO) is a known vasodilator, bronchodilator, anti-inflammatory and anti-microbial agent, opening a new approach in the treatment of viral lower respiratory tract infections

METHODS:

- A prospective, multi-center, double-blind, randomized study
- Inclusion criteria included infants up to 12-months old with acute bronchiolitis requiring in-patient hospitalization expected to last 24 hours or more
- Primary objective: **to assess whether NO administered in two concentrations in addition to Standard Supportive treatment (SST) shortens the recovery time of infants with bronchiolitis, compared to SST alone**
- A total of **89 subjects** were enrolled into the study and randomized (Figure 1) to receive inhalations of either 150 ppm NO, 85 ppm NO or control (1:1:1)
- Study treatment was given for 40 minutes, every 4.5 hours (±30 min), 4 times/day, for up to 5 days
- Pairwise treatment group comparison, was analyzed by Cox proportional hazards regression stratified by site with terms for pre-term birth (yes/no), age, and background variables as covariates; the treatment effect was measured by the hazard ratio

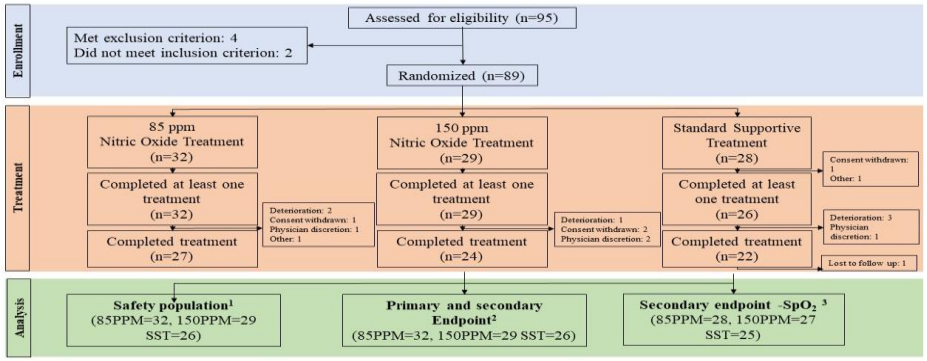
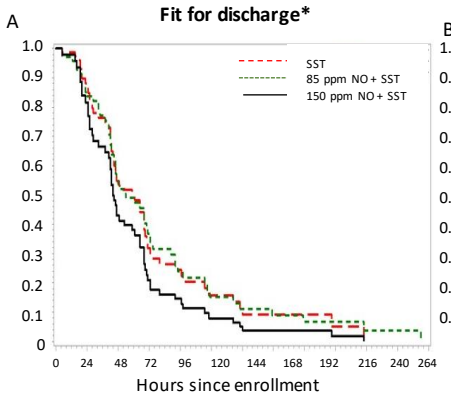
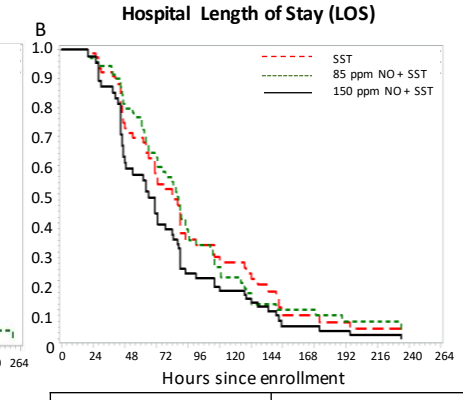


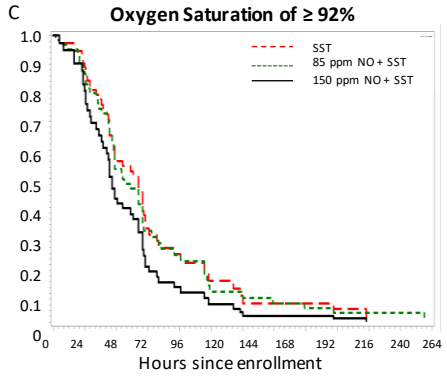
Figure 1. Recruitment and Randomization of Study Patients: subjects were randomized to three groups: SST, 85 ppm Nitric Oxide treatment + SST and 150 ppm Nitric Oxide treatment + SST. 89. ITT population included patients receiving at least 1 inhalation (n=87).

RESULTS:

- A statistically significantly shortening in the recovery time of infants with bronchiolitis was achieved for the 150 ppm NO arm when compared to 85 ppm NO and when compared to the control treatment arm. No statistical difference was observed between 85 ppm NO and control (Figure 2).
- There were no events of $NO_2 \geq 3$ ppm or MetHb > 7% in either group (Figure 3), and no SAEs were found related to study treatment (Table 1)

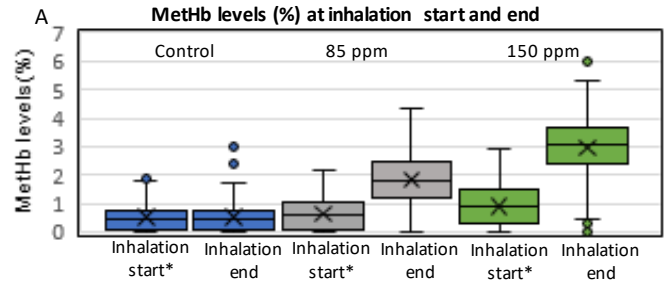






150 ppm vs. 85 ppm Hazard Ratio (P-value)	150 ppm vs. SST Hazard Ratio (P-value)
Fit for Discharge*	
2.11 (0.041)	2.32 (0.049)
Hospital Length of Stay (LOS)	
2.01 (0.046)	2.28 (0.043)
Oxygen Saturation of ≥ 92%	
2.15 (0.0555)	2.62 (0.0392)

Figure 2- Probability of achieving fit for discharge over time (panel A), probability of achieving hospital discharge (Panel B) and probability of achieving oxygen saturation of ≥92% (Panel C) Probability curves adjusted for baseline onset of symptoms before hospital. Admission of at least 80 hours vs < 80 hours, wheezing score of severe/moderate vs. mild/normal, SpO2 score of severe/moderate vs. mild/normal, accessory score of severe/moderate vs. mild/normal. Analysis was performed in the ITT population. ***Fit for Discharge** is a composite endpoint of clinical signs and symptoms to indicate readiness to be evaluated for hospital discharge.



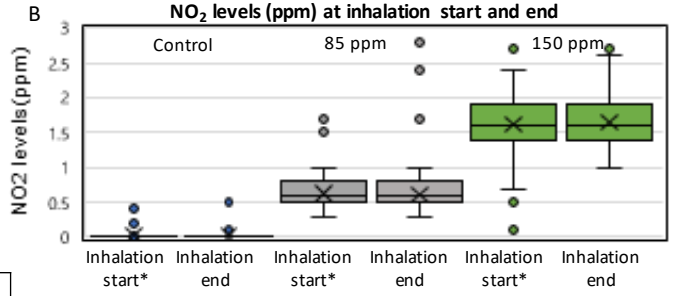


Figure 3- MetHb and NO_2 levels at inhalation start and end
Pooled MetHb (panel A) and NO_2 entering the breathing mask (panel B) at inhalation start and inhalation end for all treatments in all groups (control, 85 ppm and 150 ppm) are shown in box-whisker plots. Boxes display 25th to 75th percentile, middle line represents the median, and outliers are presented as dots* **Inhalation start = 1-2 minutes from treatment administration start**

Table 1. Summary of Adverse Events per treatment group

	SST (N=26)		85 ppm NO + SST (N=32)		150 ppm NO + STT (N=29)	
	N	%	N	%	N	%
Any AE	13	50.0	20	62.5	18	62.1
Any SAE	1	3.8	1	3.1	3	10.3
Any AE Leading to Study Treatment discontinuation	2	7.7	2	6.3	3	10.3
Any AE Leading to Study treatment temporary discontinuation	0	0.0	1	3.1	1	3.4
Any AE Classified as Severe	1	3.8	2	6.3	1	3.4
Any SAE Drug-related	0	0.0	0	0.0	0	0.0

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Conclusion: The effects of intermittently inhaled NO (iNO) at 150 ppm on reducing LOS and rapidly improving respiratory outcome in infants with bronchiolitis were statistically significant compared with both standard therapy and 85 ppm iNO. All treatments had similar safety profiles and were well tolerated.