Long-term Effects of Inhaled Nitric Oxide in Infants with Bronchiolitis – A Multi Center Study

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Disclosure

Prof. Aviv Goldbart

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- This study was funded by Beyond Air Inc.

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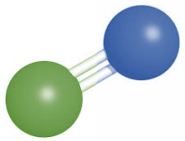
Inhaled Nitric Oxide (iNO) for the treatment of Bronchiolitis

- **Acute Bronchiolitis**
  - Leading cause of infant hospitalizations, accounting for >120,000 hospitalizations with a direct cost of at least $550 million each year[1]
  - Limited treatment options exist and mainly rely on supportive treatment
- **Inhaled NO (iNO)**
  - Approved by FDA and EMA for use in **ventilated** patients for the treatment of pulmonary hypertension in neonates (continuous flow of 20 ppm) and for pulmonary heart disease and persistent pulmonary hypertension in all age groups (20-40 ppm) in Europe
  - For the purpose of this study, this was an **investigational drug that was inhaled through a breathing mask**



1. Hasegawa et al. Trends in bronchiolitis hospitalizations in the United States, 2000-2009. Pediatrics 2013, 132(1):28-36.

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iNO in Bronchiolitis

- Three randomized double blind clinical trials were conducted with high intermittent dose of iNO for acute bronchiolitis.
- In these studies, iNO inhalations or Oxygen/air (control) were administered in addition to Standard Supportive Treatment (SST).

Study Number	Year	Number of sites	NO dose and frequency	Number of subjects
Study 1 NCT01768884	2012-2013	1	160 ppm, 30 min 5 times/day	n=43 **single center** (iNO: n=21, SST: n=22)
Study2 NCT03053388	2016-2018	6	160 ppm, 30 min 5 times/day	n=68 **multi-center** (iNO: n=34, SST: n=34)
Study 3 NCT04060979	2019-2020	8	85 ppm /150 ppm, 40 min 4 times/day	n=87, **multi-center** (iNO-85ppm: n=32, iNO-150ppm: n=29 , SST: n=26)

- Total number of 150/160 ppm iNO treated infants was 84

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Publications

iNO in Bronchiolitis

Study 1
NCT01768884

Received: 2 August 2017 | Accepted: 11 October 2017
DOI: 10.1002/ppul.23905

ORIGINAL ARTICLE: RESPIRATORY INFECTIONS

WILEY

Nitric oxide inhalations in bronchiolitis: A pilot, randomized, double-blinded, controlled trial

Asher Tal[1,2,3] | David Greenberg[2,3,4] | Yossef Av-Gay[3,5] | Inbal Golan-Tripto[1,2] | Yael Feinstein[1,2] | Shalom Ben-Shimol[2,4] | Ron Dagan[2] | Aviv D. Goldbart[1,2]

Study 2
NCT03053388

SCIENTIFIC REPORTS
nature research
Check for updates

OPEN

Inhaled nitric oxide therapy in acute bronchiolitis: A multicenter randomized clinical trial

Aviv Goldbart[1], Inbal Golan-Tripto[1], Giora Pillar[2], Galit Livnat-Levanon[2], Ori Efrati[3], Ronen Spiegel[4], Ronit Lubetzky[5], Moran Lavie[5], Lior Carmon[1] & Amit Nahum[1]

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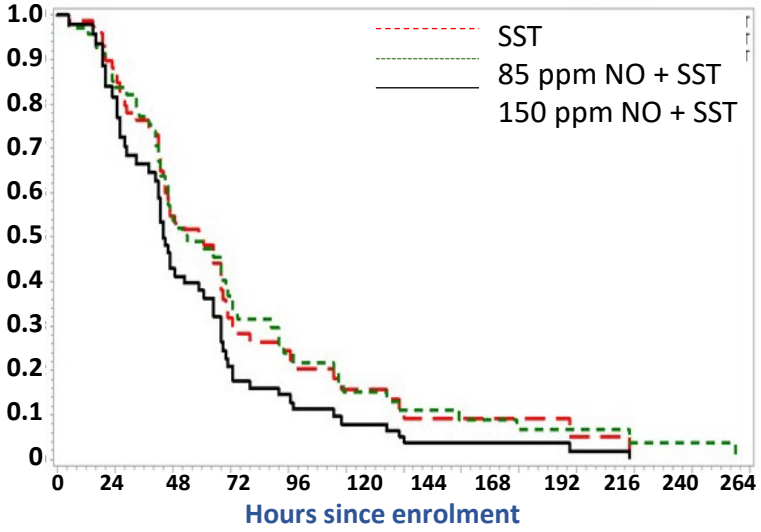
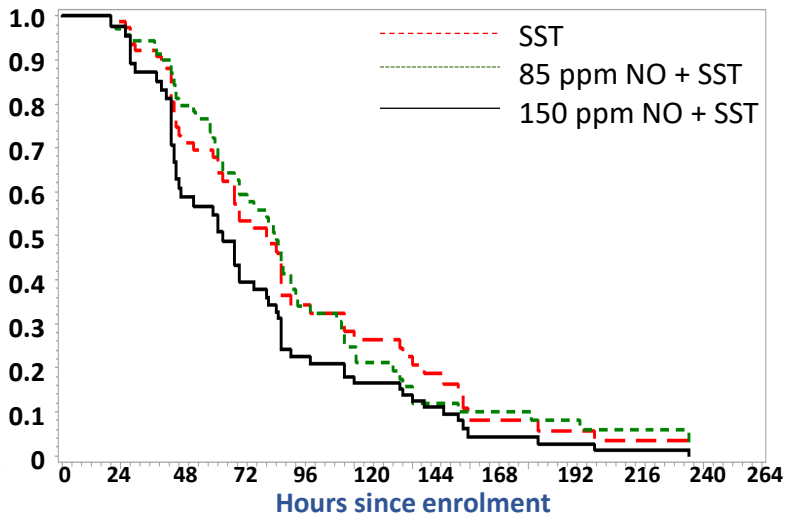
Benefits of High Dose iNO Treatment

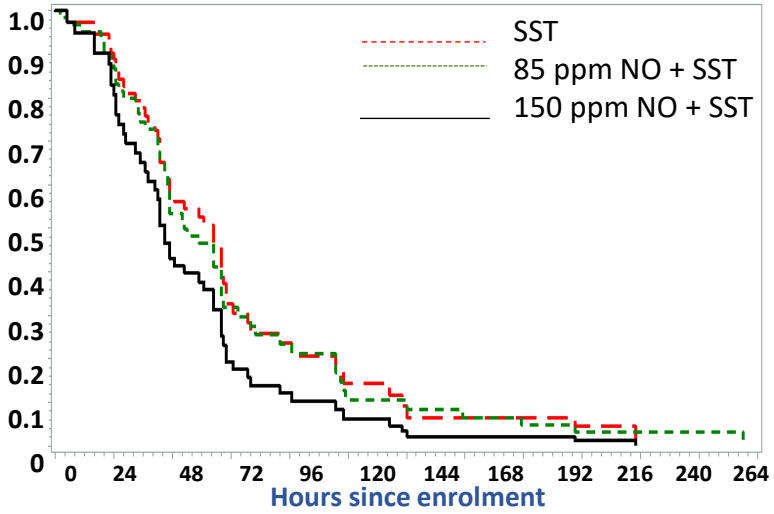
Fit for discharge*



Hospital Length of Stay (LOS)



Oxygen Saturation of ≥ 92%



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)

***Fit for Discharge** is a composite endpoint of clinical signs and symptoms to indicate readiness to be evaluated for hospital discharge

Study 3
NCT04060979

Goldbart *et al.*, pending publication

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Short term effect of iNO treatment

- All three studies showed a favorable short term safety profile:
  - **No iNO-treatment related Serious Adverse Events (SAEs) or severe AEs were reported**
  - **The incidence level for severe AEs was similar among all groups**

- Data from previous trials suggest that iNO has a favorable long-term safety profile, though this has not been tested on 150/160 ppm iNO administered intermittently for several days.
- The purpose of this study is to determine **the long-term effects of high dose iNO treatment in bronchiolitis** patients enrolled in the three bronchiolitis studies.

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Trial Overview

Study	Long-Term, Non-interventional, Multi-center for longitudinal data collection
Participants	Children who previously participated in three past clinical trials using iNO (treatment) or Oxygen/air (control) for treatment of acute bronchiolitis .
Study Measures	Data collected based on parent interview and medical records review
Study Endpoints	• Percentage of subjects re-hospitalized for bronchiolitis related reasons • Percentage of subjects re-hospitalized for any reason

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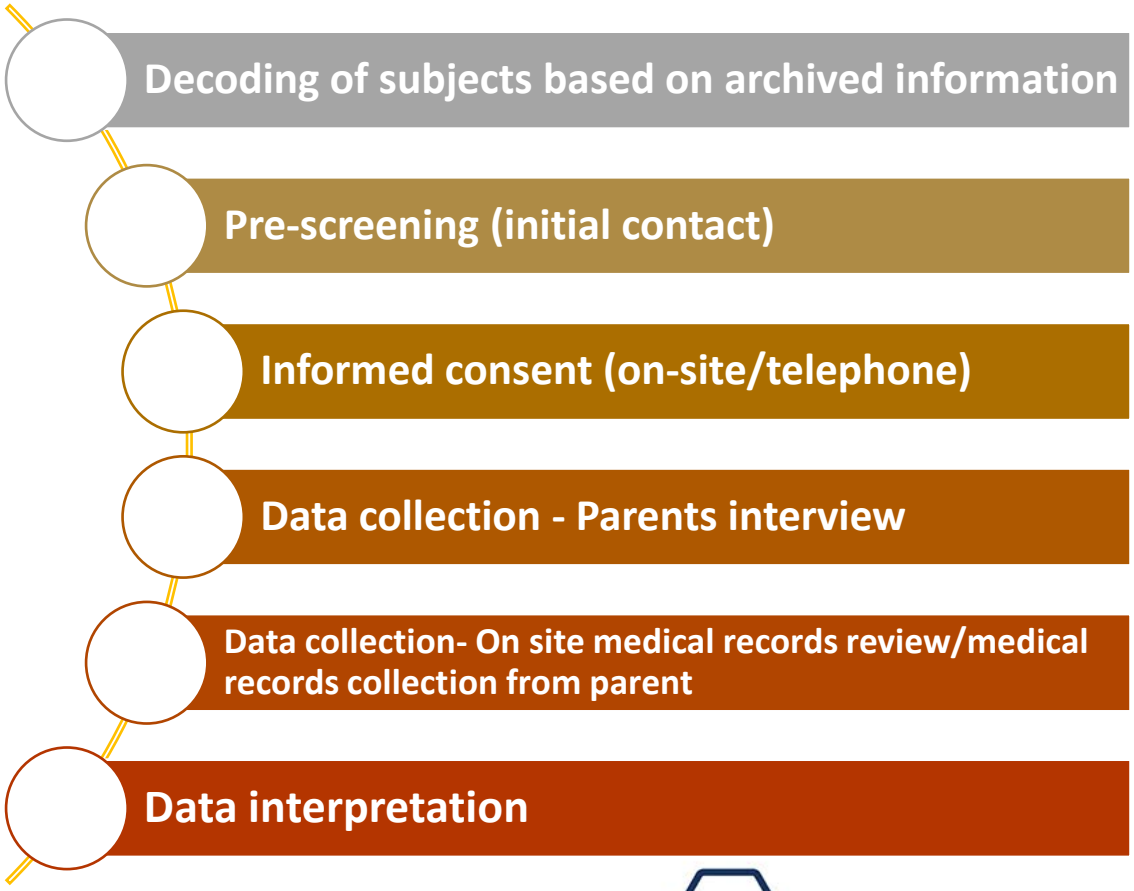
Study design

- This non interventional study was designed to collect longitudinal data about the **frequency and cause of hospital readmissions.**

- Data were collected from participants of the three past double-blind randomized clinical trials that evaluated the treatment of bronchiolitis, by intermittent high dose iNO



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RESULTS

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Study Population

- Out of 198 potential participants in 10 potential sites, 101 subjects were enrolled in 6 sites

Study 1 (N = 43) 2013/2014		Study 2 (N = 68) 2017/2018		Study 3 (N = 87) 2019/2020			Total enrolled				
N enrolled = 13		N enrolled = 29		N enrolled = 59			N enrolled = 101				
SST	iNO 160 ppm	SST	iNO 160 ppm	SST	iNO 150 ppm	iNO 85 ppm	SST	iNO 160 ppm	iNO 150 ppm	iNO 85 ppm	Total iNO
N=7	N=6	N=17	N=12	N=15	N=20	N=24	N=39	N=18	N=20	N=24	N=62

Mean Follow-Up Time

SST – 3.2 years; 85ppm – 1.6 years ; 150 ppm – 1.5 years ; 160ppm – 4.7 years

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Baseline Demographics

Gender	SST (N=39)		85 ppm iNO + SST (N=24)		150 ppm iNO + SST (N=20)		160 ppm iNO + SST (N=18)		Total (N=101)	
	N	%	N	%	N	%	N	%	N	%
Female	14	35.9	13	54.2	6	30.0	6	33.3	39	38.6
Male	25	64.1	11	45.8	14	70.0	12	66.7	62	61.4

Treatment Group/Age at Enrollment (Yrs.)	SST (N=39)	85 ppm iNO + SST (N=24)	150 ppm iNO + SST (N=20)	160 ppm iNO + SST (N=18)	Total (N=101)
Mean	4.0	2.0	2.0	5.5	3.4
Std	2.3	0.2	0.3	2.2	2.2
Min	1.8	1.6	1.7	3.7	1.6
Median	3.7	1.9	1.8	4.1	2.4
Max	9.2	2.5	2.8	9.1	9.2

- Majority of enrolled infants was males
- Infants mean age at follow up was of 3.4 years, with ages ranging from 1.6 to 9.2 years

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Long Term Safety Profile of iNO

Subjects re-hospitalized for bronchiolitis related outcomes

Treatment /Control Group	Subjects re-hospitalized (N)	Total Subjects (N)	Incidence Rate (95%CI) (%)	PEY*	Rate per 100 PEY (95%CI)
SST	6	39	15.39 (5.86 to 30.53)	143.0	**4.20** (1.60 to 8.33)
85 ppm iNO + SST	1	24	4.17	38.0	**2.63**
150 ppm iNO + SST	1	20	5.00	32.4	**3.09**
160 ppm iNO + SST	2	18	11.11 (1.38 to 34.71)	90.6	**2.21** (0.27 to 6.90)

Subjects re-hospitalized for any reason

Treatment Group	Subjects re-hospitalized (N)	Total Subjects (N)	Incidence Rate (95%CI) (%)	PEY	Rate per 100 PEY (95%CI)
SST	8	39	20.51 (9.30 to 36.46)	143.0	**5.59** (2.54 to 9.95)
85 ppm iNO + SST	5	24	20.83 (7.13 to 42.15)	38.0	**13.16** (4.50 to 26.62)
150 ppm iNO + SST	2	20	10.00 (1.24 to 31.70)	32.4	**6.17** (0.76 to 19.57)
160 ppm iNO + SST	3	18	16.67 (3.58 to 41.42)	90.6	**3.31** (0.71 to 8.23)

- Participants' re-hospitalization **rate** per 100 Patient Exposure Years (PEY), due to bronchiolitis related reasons trended favorably for the iNO group
- No significant difference was demonstrated in the **rate** of subjects re-hospitalized for any reason
- No trends in hospitalization reasons were observed

*PEY=Patient Exposure Years, It is anticipated that the follow-up time when subjects completed the original studies to this current study will be different for different subjects. It is, therefore, necessary to calculate the patient year (PEY) which is the summation of the time (in years) from original study completion date to date of participation in the current study

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In summary

- Our studies have suggested benefits of iNO treatment for bronchiolitis demonstrated by a shorter Length of Hospital Stay (LOS) and shorter time of oxygen dependence (Time to room air SaO2≥92%)
- Short term safety effects of iNO in acute bronchiolitis (up to 30 days) showed no drug related Serious Adverse Events (SAEs) or severe AEs
- Long term subject rehospitalization rate for any reason was similar between iNO and control groups

Conclusion

- The findings from this study suggest that the treatment of hospitalized infants with acute bronchiolitis by intermittent high dose inhaled Nitric Oxide show a favorable long-term safety profile

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Thank You

Q&As

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