Cost-effectiveness of Inhaled Nitric Oxide for Treatment of Infants with Hypoxic Respiratory Failure: Initiation at Hospital of Birth vs. Helicopter Transfer to Another Hospital

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BACKGROUND

Background

- Neonatal respiratory failure occurs in approximately 2% of all live births and is responsible for one in three neonatal deaths.[1]
- Inhaled nitric oxide (iNO) is a pulmonary vasodilator that is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation (ECMO) among term and near-term neonates (>34 weeks gestation), who experience hypoxic respiratory failure associated with pulmonary hypertension, in conjunction with ventilatory support and other appropriate agents.[2]
- Guidelines from the American Heart Association and American Thoracic Society recommend that treatment with iNO be initiated once the patient has an oxygenation index (OI) ≥25, and that ECMO rescue be initiated if there is continued progression to OI ≥40.[3]
- The efficacy of iNO initiated earlier in the treatment paradigm has been evaluated, and has been shown to provide additional clinical improvement with respect to decreased need for ECMO and improved survival rates.[4-8]
- Early initiation of iNO at an OI of 15-19 is cost-effective compared to delayed initiation at an OI ≥25;[9] however, early initiation is often not possible because iNO is not available in all US hospitals.

Objective

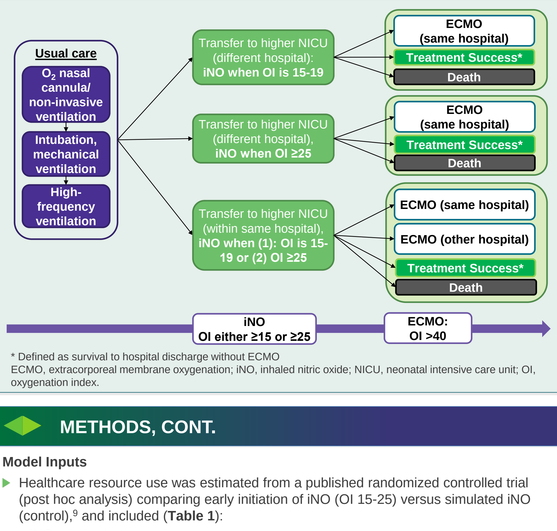
- The objective of this model was to compare the cost-effectiveness of early initiation of iNO when OI is 15-19 or delayed initiation when OI is ≥25, either at the hospital of birth or after transfer to an iNO hospital via helicopter emergency services (HES).

METHODS

Model Design

- The decision analytic model evaluated the costs and effectiveness of early initiation of iNO at the birth hospital vs. transfer to an iNO hospital via HES over a 12-month time horizon from the healthcare system perspective.
- The model compares clinical and economic outcomes associated with each of the three scenarios (**Figure 1**):
  1. At OI level 15-19, transfer patients to another hospital for iNO
  2. At OI level ≥25, transfer patients to another hospital for iNO
  3. At OI level 15-19 or ≥25, transfer patients to a higher level neonatal intensive care unit (NICU) within the birth hospital for iNO

Figure 1. Model Treatment Pathway



* Defined as survival to hospital discharge without ECMO

ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide; NICU, neonatal intensive care unit; OI, oxygenation index.

METHODS, CONT.

Model Inputs

- Healthcare resource use was estimated from a published randomized controlled trial (post hoc analysis) comparing early initiation of iNO (OI 15-25) versus simulated iNO (control),[9] and included (**Table 1**):
  - iNO administration, in hours
  - Hospital days, categorized according to resources required:
    - NICU days receiving ECMO and mechanical ventilation (MV)
    - NICU days receiving only MV
    - NICU days with no ECMO nor MV
    - Non-NICU days
  - Hospital transfer via HES
- Clinical outcomes at hospital discharge were obtained from the same source and categorized as (**Table 2**):
  - Survive without ECMO (treatment success)
  - Survive with ECMO
  - Death
- Unit costs for hospital resources were obtained from a previously published cost-effectiveness model comparing treatment with and without iNO, which estimated costs at 4 ECMO centers[10]
  - Unit costs were converted to 2018 US$ using the Consumer Price Index for Medical Care[11]
- Cost of HES transfer was estimated from Medicare data,[12] and includes:
  - Base rate for helicopter transport
  - Cost per mile
  - Advanced life support provided on the helicopter

Table 1. Healthcare Resource Use Inputs

	Early iNO	Delayed iNO	Reference
iNO, hours			
Treatment success	113.9	50.4	Konduri et al.[9]
Survival following ECMO	117.9	44.0	
Death	111.5	167.5	
NICU days with ECMO and MV			
Treatment success	--	--	Konduri et al.[9]
Survival following ECMO	8.4	5.0	
Death	2.5	6.7	
NICU days with only MV			
Treatment success	10.5	9.7	Konduri et al.[9]
Survival following ECMO	13.1	9.5	
Death	16.8	13.9	
NICU days no ECMO or MV			
Treatment success	17.9	27.6	Konduri et al.[9]
Survival following ECMO	15.0	8.0	
Death	5.7	0.4	
Non-NICU days			
Treatment success	1.0		Angus et al.[10]
Survival following ECMO	1.0		
Hospital transfer, % of patients			
Transfer to iNO-ECMO hospital	100%		Angus et al.[10]
Transfer to ECMO hospital	79%		

ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide; MV, mechanical ventilation; NICU, neonatal intensive care unit; OI, oxygenation index.

Table 2. Clinical Inputs

	Early iNO	Delayed iNO	Reference
Survive without ECMO (treatment success)	89.8%	82.6%	Konduri et al.[9]
Survive with ECMO	6.8%	8.7%	
Death	3.4%	8.7%	

METHODS, CONT.

Model Outcomes

- The primary outcome was incremental cost-effectiveness ratio, calculated as the difference in total costs divided by the difference in ECMO-free survival.
- Costs are reported in 2018 US dollars.

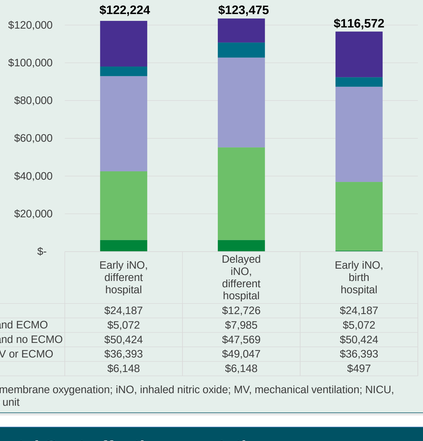
Model Assumptions

- All patients receive the same usual care consisting of O_2 via nasal cannula/non-invasive ventilation, intubation, mechanical ventilation, and high-frequency ventilation before being considered for iNO treatment.
- All patients receive iNO for a fixed amount of time, and any additional medications administered during the hospitalization would not affect the clinical endpoints.
- Adverse events are not different across model arms, therefore, the healthcare resource utilization and costs of adverse events are not incorporated into the model.
- HES do not affect any model outcomes with exception of costs.
- Patients who receive iNO at the hospital of birth may still require HES transfer for ECMO if it is not available at that hospital.

RESULTS

- Total costs per patient were lowest when iNO was initiated early at the hospital of birth ($116,572), followed when iNO was initiated early after hospital transfer ($122,224) and when initiation was delayed after HES transfer ($123,475).
- Compared to early initiation of iNO at the birth hospital, delayed initiation after HES transfer was associated with lower iNO costs but higher hospitalization, ECMO, and transport costs (**Figure 2**).
- Because clinical outcomes are the same in patients receiving early iNO regardless of HES transfer, only transport costs differ between these groups, with a cost savings of $5,651 per patient when iNO is available at the birth hospital (**Table 3**).
- Early initiation of iNO at the birth hospital resulted in a cost savings of $6,902 per patient compared to late initiation of iNO after HES transfer, with an increase in probability of ECMO-free survival of 0.072, and thus was economically dominant.

Figure 2. Cost by Treatment Arm and Type



	Early iNO, different hospital	Delayed iNO, different hospital	Early iNO, birth hospital
iNO	$24,187	$12,726	$24,187
NICU days with MV and ECMO	$5,072	$7,985	$5,072
NICU days with MV and no ECMO	$50,424	$47,569	$50,424
Hospitalization, no MV or ECMO	$36,393	$49,047	$36,393
Hospital transfer	$6,148	$6,148	$497

ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide; MV, mechanical ventilation; NICU, neonatal intensive care unit

Table 3. Incremental Cost-effectiveness Ratio

	Δ Costs	Δ ECMO-free survivors	ICER
Early iNO (birth hospital) vs early iNO (different hospital)	-$5,651	0.000	Cost-saving
Early iNO (birth hospital) vs delayed iNO (different hospital)	-$6,902	0.072	Economically dominant

ECMO, extracorporeal membrane oxygenation; ICER, incremental cost-effectiveness ratio; iNO, inhaled nitric oxide

LIMITATIONS

- Healthcare resource utilization was derived from small samples, especially for patients who survived following ECMO and/or experienced death.
- Due to a lack of more contemporary data, healthcare unit costs were sourced from an analysis conducted in 2003 and inflated to current year costs.
- The effect of any additional treatments received by patients that could influence clinical outcomes, changes in the treatment paradigm from the time that the clinical trials were performed, and any influences HES transfer may have on clinical outcomes were not included in the model due to the absence of supporting evidence.

CONCLUSIONS

- Early initiation of iNO at an OI of 15-19 at the hospital of birth is cost-saving compared to HES transfer, provided that the transfer does not delay iNO initiation.
- Assuming that HES transfer for iNO initiation results in delayed initiation, availability of iNO at the hospital of birth is associated with lower costs and improved ECMO-free survival compared to HES transfer for iNO initiation.
- Hospitals that do not currently have iNO available can realize substantial cost savings by implementing protocols to initiate iNO at an OI of 15-19.

DISCLOSURE

- This study was sponsored by Mallinckrodt Pharmaceuticals.

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