Neonatal ventilation with inhaled nitric oxide versus ventilatory support without inhaled nitric oxide for preterm infants with severe respiratory failure: the INNOVO Multicentre Randomised Controlled Trial (ISRCTN 17821339)


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The authors studied the use of ventilation with inhaled nitric oxide (iNO). The starting dose was 5 parts per million, doubling to 10, 20 and 40 parts per million until a satisfactory dose was achieved. The minimum possible effective dose was found using reverse dose-response weaning.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised infants of less than 34 weeks' gestation, aged younger than 28 days and with severe respiratory failure requiring ventilatory support (and having had surfactant when appropriate). Infants were only included if the responsible clinician was uncertain about whether the infant might benefit from iNO. Infants were excluded if they had congenital heart disease, evidence of uncorrectable bleeding disorder, or a contraindication to the continuation of all intensive care.

Setting
The setting was secondary care. The economic study was carried out in the UK and the Republic of Ireland.

Dates to which data relate
The effectiveness data related to patients recruited between February 1997 and December 2001. The resource use data referred to the same time. The price year was 2002/03.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively using the same sample of patients as that used in the effectiveness study.

Study sample
The study sample comprised 108 infants from 15 neonatal units across the UK and Ireland. Fifty-five infants were allocated to receive iNO and 53 were allocated to not receive iNO. Power calculations had been carried out. These
indicated that a sample size of 200 preterm infants was required to ensure 80% power with a significance level of 0.05. The sample was selected by including infants admitted to eligible hospitals. A hospital was eligible if it was accustomed to providing long-term ventilatory support for newborn infants, had facilities to provide iNO, and had research ethics committee approval to participate. There were no reports of refusal to participate.

**Study design**
The authors designed a randomised controlled trial across 15 neonatal units in Ireland and the UK. Clinicians and parents were not blinded to the allocated group although, where possible, outcomes were assessed without knowledge of either the randomised or actual treatment. The infants were followed for 1 year. Sixty-four patients died before follow-up and one patient was lost to formal follow-up.

**Analysis of effectiveness**
The analysis was based on intention to treat principles. Three infants randomised to iNO did not receive iNO (died before administration), while 4 patients randomised to not receive iNO did receive iNO (all 4 of whom later died). The primary health outcomes were assessed at discharge from neonatal services (or prior death) and at 1 year corrected age. The outcomes assessed were death or severe disability at 1 year corrected age (assessed individually and as a composite measure) and death before discharge or chronic lung disease. The infants in the two groups were compared extensively at baseline in terms of their demographic and clinical variables. Infants in the iNO group were reported to be of higher birth weight and more mature but were otherwise comparable to infants in the no iNO group.

**Effectiveness results**
The relative risk of death or severe disability at 1 year corrected age was 0.99 (95% confidence interval, CI: 0.76 to 1.29; p=0.94).

The relative risk of death or supplemental oxygen on expected date of delivery was 0.84 (95% CI: 0.68 to 1.02; p=0.08).

The relative risk of death was 0.85 (95% CI: 0.62 to 1.16; p=0.30).

**Clinical conclusions**
The authors concluded "there was no evidence of an effect of iNO on any of the pre-specified primary outcomes: death or severe disability at 1 year corrected age".

**Measure of benefits used in the economic analysis**
The authors did not estimate a summary measure of health benefit. The study was, in effect, a cost-consequences analysis.

**Direct costs**
A perspective for the cost analysis was not reported, although the authors noted that costs to a range of agencies were included. The principle elements included in the analysis were length of stay in the hospital, length of time on supplemental oxygen, and length of time on ventilatory support. These data were collected for the first stay in hospital on specially designed data collection sheets. Data concerning health and community service use and costs to parents between discharge home and 1 year corrected age were obtained from cross-sectional questionnaires completed by parents at 6-monthly intervals. The unit costs were taken from the National Health Service reference costs database and from published sources. The price year was 2002/03. Discounting was not required because of the relatively short time horizon of the study. Missing data from parent report forms were assumed to have the mean value of community costs from the survivors from the treatment or control groups.
Statistical analysis of costs
Statistical analyses were carried out. These reported 95% CIs derived from non-parametric bootstrapping to allow for the skewed distribution of the costs.

Indirect Costs
No indirect costs were included.

Currency
UK pounds sterling (£). A conversion rate of 1.00 = US$1.56 in 2003 was noted.

Sensitivity analysis
Sensitivity analyses were carried out, although the authors did not state the overall aim of these analyses or how they determined the ranges to be used. For instance, the base-case cost per hospital day for Level 1 neonatal care was 793 and the sensitivity value was 946.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The mean cost of NO was 1,777 (standard deviation, SD=1,200) for iNO and 167 (SD=654) for no iNO. The difference was 1,610 (95% CI: 1,239 to 1,980).

The mean cost of initial hospitalisation was 30,442 (SD=35,389) for iNO and 18,501 (SD=20,367) for no iNO. The difference was 11,941 (95% CI: 184 to 23,699).

The mean cost of subsequent hospitalisation was 1,312 (SD=4,357) for iNO and 563 (SD=1,444) for no iNO. The difference was 749 (95% CI: -499 to 1,997).

The mean cost of outpatient services was 946 (SD=1,836) for iNO and 623 (SD=1,232) for no iNO. The difference was 322 (95% CI: -277 to 921).

The mean cost of general practitioner and community services was 771 (SD=1,463) for iNO and 420 (SD=123) for no iNO. The difference was 351 (95% CI: -114 to 815).

The mean of personal costs was 58 (SD=154) for iNO and 117 (SD=546) for no iNO. The difference was -58 (95% CI: -210 to 94).

The mean total cost was 35,306 (SD=35,941) for iNO and 20,391 (SD=26,680) for no iNO. The difference was 14,915 (95% CI: 2,803 to 27,026).

Synthesis of costs and benefits
Not relevant.

Authors’ conclusions
The study did not find beneficial effects of inhaled nitric oxide (iNO). There was some evidence of greater costs associated with iNO.

CRD COMMENTARY - Selection of comparators
The authors compared the use of ventilation with and without iNO. They noted that previous trials had failed to show statistically significant medium and longer term outcomes and suggested that this was due to the small sample sizes. The reader must assess whether these comparators are appropriate in their own setting.

**Validity of estimate of measure of effectiveness**
The authors designed a randomised controlled trial to try to reduce the likelihood of systematic differences between infants in the two groups. Despite this, infants in the iNO group were reported to be of higher birth weight and more mature. Although the authors did not address these potentially confounding factors, they argued that these factors would reduce the difference between iNO and no iNO infants and so their analysis provided a conservative estimate of effectiveness. For future analyses the authors might attempt to stratify the randomisation, or use statistical analysis to account for the potential biases introduced.

**Validity of estimate of measure of benefit**
The authors did not produce a summary measure of health benefit. The study was, in effect, a cost-consequences analysis.

**Validity of estimate of costs**
The authors did not state the perspective from which the costs were estimated. Therefore, it is not possible to assess whether all the relevant costs were included. However, the authors provided a full breakdown of resource use and unit costs, thereby enabling the reader to gain a thorough understanding of the structure and key cost-drivers and also improving the generalisability of the analysis. Further detail on how the ranges for the sensitivity analysis were determined would have been useful.

**Other issues**
The authors suggested that their results are "largely in keeping with those from existing trials". The issue of generalisability to other settings was not explicitly addressed but was improved by the use of sensitivity analyses and the inclusion of multiple centres. The results were presented thoroughly, thus enabling the reader to draw their own conclusions. The authors' conclusions were consistent with the result reported and related well to the scope of the study. Several limitations were noted. These focused on the failure to reach the target study sample size (200 infants), the lack of blinding, and the fact that infants were given other treatments which may have acted as confounding variables. In addition, the severe illness of the youngsters might have meant that treatment was introduced too late to be of help. The authors explored the low recruitment rate in depth, thus allowing the reader to understand the reasons for this.

**Implications of the study**
The authors noted that some studies were already taking place in the USA to explore whether iNO might have more beneficial effects in less ill, pre-term infants than those studied in this trial. The authors suggested that the results of these studies will have policy implications.

**Source of funding**
None stated.

**Bibliographic details**

**PubMedID**
Other publications of related interest
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Indexing Status
Subject indexing assigned by NLM

MeSH
Administration, Inhalation; Combined Modality Therapy; Developmental Disabilities /epidemiology; Disabled Children; Female; Health Care Costs; Health Resources /utilization; Humans; Infant, Newborn; Infant, Premature; Infant, Premature, Diseases /mortality /therapy; Length of Stay; Lung Diseases /epidemiology; Male; Nitric Oxide /economics /therapeutic use; Respiration, Artificial; Respiratory Insufficiency /complications /mortality /therapy; Treatment Failure

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