Neonatal ventilation with inhaled nitric oxide vs ventilatory support without inhaled nitric oxide for infants with severe respiratory failure born at or near term: the INNOVO multicentre randomised controlled trial


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.

CRD summary
This study investigated the costs and clinical benefits of treating infants, who were born at or near term and had severe respiratory failure, with inhaled nitric oxide plus ventilatory support compared with ventilatory support alone. The authors concluded that the addition of inhaled nitric oxide was likely to be cost-effective, as it produced similar effects at lower costs than ventilatory support alone. The methods were transparent, thorough and appropriate, however further research is required to support the authors' conclusion.

Type of economic evaluation
Cost-effectiveness analysis

Study objective
The aim was to examine the costs and effects of neonatal ventilation, with inhaled nitric oxide (iNO), for infants with severe respiratory failure, born at or near term.

Interventions
This study assessed the cost and effects of iNO compared with ventilatory support without iNO for babies, born at or near term, with severe respiratory failure. The study population comprised infants, born at 34 weeks gestation or more, aged less than 28 days, who had severe respiratory failure, which required ventilatory support, and who had received surfactant where appropriate. The attending clinician was also required to be uncertain as to whether the infant would benefit from iNO.

Location/setting
UK, Finland, Ireland and Belgium/in-patient care in fifteen neonatal units.

Methods
Analytical approach:
The evaluation was based on the first year of data from a multi-national clinical trial. The authors stated that the perspective was that of the hospital.

Effectiveness data:
The study was a non-blinded randomised controlled trial (RCT) located at multiple sites. The patients were followed-up at one year old (corrected for prematurity) and the primary outcomes were death and severe disability. Secondary outcomes were the length of stay in hospital, length of time on supplemental oxygen, length of time on ventilatory support, and extra-corporeal membrane oxygenation (ECMO) support. An intention-to-treat analysis was conducted and the two treatment groups were reported to be broadly comparable at baseline and at the one-year assessment.

Monetary benefit and utility valuations:
Not applicable.

Measure of benefit:
The primary clinical outcomes were death and severe disability.
Cost data:
The resources were measured and valued for the initial hospital stay, which included the duration of iNO, ECMO, ventilation, and oxygen therapy. The health utilisation data were derived from specially developed trial datasheets. The hospitalisation unit costs were from the National Health Service (NHS) reference costs database. The unit costs of ECMO were from a published cost analysis. The results were presented in 2002 to 2003 UK pounds sterling (£). Non-parametric bootstrapping methods were used with 200 replications to calculate the mean costs and 95% confidence intervals (CIs).

Analysis of uncertainty:
The 95% CIs were indicative of the level of uncertainty around the cost and quantity estimates. A one-way sensitivity analysis was performed on a few variables, which included low and high nitric oxide cost, low ECMO cost, higher neonatal intensive care cost, and adding ECMO transportation costs.

Results
No statistically significant differences between the two groups were found, for the primary outcomes of number of deaths or severe disabilities, by the corrected age of one year (relative risk: 0.96, 95% CI: 0.46 to 2.03). There were also no significant differences in the time to death nor the short-term measure of death or supplemental oxygen at 28 days (relative risk: 0.84, 95% CI: 0.46 to 1.54).

The total mean hospitalisation cost for iNO was £18,929 and for no iNO was £20,425. The mean difference was -£1,497 in favour of iNO, but the 95% CI (-14,472 to 11,478) was wide and spanned zero. Sensitivity analyses found very little change in the total costs and cost differences, between the two groups, in the base analysis.

There was no synthesis of costs and benefits.

Authors’ conclusions
The authors concluded that, although the use of iNO had similar clinical outcomes compared with no iNO, it was delivered at a relatively lower cost on average, and therefore was likely to be cost-effective.

CRD commentary
Interventions:
The choice of comparator was justified because no iNO was standard practice and iNO added to the ventilatory support was the new option. As some hospitals may not have the facilities for providing iNO, the reader should decide if the use of iNO represents a viable option in their own setting.

Effectiveness/benefits:
The analysis was based on a RCT, which is considered to be the ‘gold standard’ study design. One participant was lost to follow-up at the one-year assessment. The sample appeared to represent the target population, suggesting good external validity, while the two groups were comparable at baseline on their key clinical and demographic characteristics. However, as highlighted by the authors, this was an opportunistic study and the power calculations were undertaken on the clinical outcomes of a different patient group in a parallel study. As a result, it is possible that the study may have had insufficient numbers to detect meaningful differences in the primary outcomes. Therefore, it is difficult to draw firm conclusions about the clinical results.

Costs:
All the relevant costs from the perspective of the hospital appear to have been included. The costs and resource quantities were reported separately and clearly in the report and included 95% CIs. Assumptions made about the unit costs were tested in sensitivity analyses, the details of which were fully reported. The methods of resource use collection, sources of unit costs, and price year were all reported.

Analysis and results:
The cost and effect results were not synthesised into cost-effectiveness ratios. Instead the authors opted to present their findings in a disaggregated manner. The findings do not appear to have been presented selectively. Despite the small sample, very detailed information on the clinical status and infant development was presented, which should enhance
the generalisability of the findings to other study samples. The authors compared their findings with two similar trials, which also suggested that iNO may be cost-effective for term infants (Neonatal Inhaled Nitric Oxide Study Group. 1997, and Clark, et al. 2000, see ‘Other Publications of Related Interest’ below for bibliographic details). However, as in this study, these two trials were also underpowered to detect meaningful differences in the clinical outcomes.

Concluding remarks:
The methodology appears to have been appropriate and was explicitly and clearly reported. Based on the results presented for costs and effects, which showed no real differences between the two groups, the authors’ conclusions should be interpreted with some caution.

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Other publications of related interest


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