Cost-effectiveness of prophylactic indomethacin in very-low-birth-weight infants

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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 use of prophylactic indomethacin in preterm very-low-birth-weight (VLBW) infants to lower the incidence of patent ductus arteriosus (PDA), intraventricular haemorrhage (IVH) and death was examined.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness and cost-utility analyses.

Study population
The study population comprised VLBW infants (less than 1,500 g).

Setting
The setting was a hospital. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were obtained from studies published between 1979 and 1998. No price year was reported.

Source of effectiveness data
The effectiveness data were derived from a review of published studies, supported by the authors' assumptions.

Modelling
A decision analytic model, constructed using a decision tree, was constructed to simulate the management of VLBW children treated with either prophylactic indomethacin or standard indomethacin. Also, to calculate the cost-effectiveness of the two treatments. A time horizon of 15 years was selected.

Outcomes assessed in the review
The health outcomes assessed in the review of the literature were the probabilities of PDA (and no PDA), medical treatment (or surgical ligation), IVH grade III/IV (or no IVH grade III/IV) and survival associated with each of these conditions. The survival associated with IVH grade III/IV was also estimated.

Study designs and other criteria for inclusion in the review
One of the primary studies was a meta-analysis. The inclusion and exclusion criteria for the review were not reported.
The authors stated that relevant randomised controlled trials, and cohort and retrospective case-control studies were included.

**Sources searched to identify primary studies**
MEDLINE was searched from 1966 to July 2000.

**Criteria used to ensure the validity of primary studies**
Not stated.

**Methods used to judge relevance and validity, and for extracting data**
Not stated.

**Number of primary studies included**
The effectiveness evidence were derived from nine primary studies.

**Methods of combining primary studies**
The studies were combined using narrative methods.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
In the prophylactic indomethacin branch, the probabilities were:

- 0.10 (range: 0.005 - 0.20) for PDA and 0.90 for no PDA;
- 0.585 (range: 0.50 - 0.70) for medical treatment and 0.415 for surgical ligation;
- 0.526 (range: 0.40 - 0.60) for IVH grade III/IV after medical treatment, and 0.474 for no IVH grade III/IV after medical treatment;
- 0.5 for survival after medical treatment and IVH grade III/IV;
- 0.80 for survival after medical treatment and no IVH grade III/IV;
- 0.742 for IVH grade III/IV after surgical ligation, and 0.258 for no IVH grade III/IV after surgical ligation;
- 0.5 for survival after surgical ligation and IVH grade III/IV;
- 0.80 for survival after surgical ligation and no IVH grade III/IV;
- 0.017 (range: 0.008 - 0.03) for IVH grade III/IV and no PDA, and 0.983 for no IVH and no PDA;
- 0.5 for survival without PDA and with IVH grade III/IV; and
- 0.96 (range: 0.90 - 1.0) for survival without PDA and no IVH.

In the standard indomethacin branch, the probabilities were:
0.32 (range: 0.20 - 0.45) for PDA and 0.68 for no PDA;

0.585 (range: 0.50 - 0.70) for medical treatment and 0.415 for surgical ligation;

0.278 (range: 0.20 - 0.40) for IVH grade III/IV after medical treatment, and 0.722 for no IVH grade III/IV after medical treatment;

0.5 for survival after medical treatment and IVH grade III/IV;

0.90 for survival after medical treatment and no IVH grade III/IV;

0.391 for IVH grade III/IV after surgical ligation, and 0.609 for no IVH grade III/IV after surgical ligation;

0.5 for survival after surgical ligation and IVH grade III/IV;

0.90 for survival after surgical ligation and no IVH grade III/IV;

0.038 (range: 0.019 - 0.067) for IVH grade III/IV and no PDA, and 0.962 for no IVH and no PDA;

0.5 for survival without PDA and with IVH grade III/IV; and

1 (range: 0.90 - 1.0) for survival without PDA and no IVH.

The survival associated with IVH grade III/IV was 3.2 years in both tree branches.

Methods used to derive estimates of effectiveness
The authors assessed the utility values required in the cost-utility analysis on the basis of expert judgement. The probability of developing an IVH in groups with and without PAD for both indomethacin and the control were obtained from discussions with experts.

Estimates of effectiveness and key assumptions
The estimated utility weight was 0.85 for patients alive without any complications and 0.4 for patients with IVH.

Measure of benefits used in the economic analysis
The benefit measures used in the economic analyses were expected survival and the quality-adjusted life-years (QALYs).

Direct costs
No discounting was conducted, although it was relevant given the time horizon of the analysis (15 years). The unit costs were not reported separately from the quantities of resources, but the cost of the indomethacin dose was reported. The economic evaluation included the costs of indomethacin, surgical ligation, intensive care nursery, IVH and death. The cost/resource boundary adopted was not stated, but appears to have been that of the health system. The costs and quantities of resources were estimated from published studies and the acquisition costs for drugs. The expected costs were calculated using the decision model. No price year was reported.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included.
Currency
US dollars ($).

Sensitivity analysis
The robustness of the estimated cost-effectiveness analysis was assessed through sensitivity analyses. The model parameters varied were the occurrence of PDA, the use of medical treatment for PDA, the probabilities of grade III and IV IVH in babies with and without PDA, and the likelihood of survival in babies without PDA and IVH. One- and two-way sensitivity analyses were performed. The variables were varied over what the authors referred to as 'plausible ranges', although no justification for these ranges was given.

Estimated benefits used in the economic analysis
The expected survival was 13 years in both tree branches. The expected QALYs were 10 in the standard treatment group and 11 in the intervention treatment group.

Cost results
Total estimated costs were $99,955 in the standard treatment group and $95,157 in the intervention treatment group.

Synthesis of costs and benefits
An incremental analysis was performed to combine the costs and the benefits. The prophylactic indomethacin treatment was dominant over standard indomethacin, as it was associated with lower costs and more QALYs gained. In terms of survival, cost-savings were observed in the intervention group in comparison with the standard treatment group. The dominance of prophylactic indomethacin was confirmed in the sensitivity analyses under reasonable conditions.

Authors' conclusions
The use of indomethacin as prophylactic therapy in the management of very-low-birth-weight (VLBW) infants proved to be a cost-effective treatment, compared with the standard indomethacin treatment. It was cost-saving and resulted in an improvement in quality-adjusted survival.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. Standard indomethacin treatment was selected as it represented the routine intervention for VLBW children. You should decide whether it is a standard treatment in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness estimates were derived from a review of published studies. The source searched to identify these studies was reported. However, the inclusion and exclusion criteria and the general methodology of the review were not described. A systematic review with clear methodology would have given more weight to the study findings. The effectiveness estimates were combined using narrative methods. It was not stated whether the authors considered the impact of differences between the primary studies.

Validity of estimate of measure of benefit
QALYs and survival were selected as the benefit measures. These appear to have been appropriately modelled. No discounting was performed. The use of QALYs enhances comparisons of the benefits of the intervention under study with other treatments funded in the health care system.
Validity of estimate of costs
The analysis was reported to have been conducted from a societal perspective. However, as the indirect costs were not included in the analysis, this appears to have been inappropriate. The unit costs were not reported (with the exception of drug costs) and no price year was given, thus hindering the reflation of the study results in other settings. The sources of the cost data were reported. Discounting was not performed but it appears to have been relevant due to the long time horizon of the analysis. The costs were treated deterministically and no sensitivity analyses were performed on the cost items included in the analysis.

Other issues
The authors did not compare their findings with those from other studies. In addition, they did not address the issue of the generalisability of the study results to other settings. The external validity of the study appears to have been low, as limited sensitivity analyses were carried out and the unit costs were not reported. The study considered VLBW babies and this was reflected in the conclusions of the analysis. The authors acknowledged some limitations of their study. These mainly related to bias due to possible confounding factors, such as the use of therapies which may have an impact on the incidence of IVH (such as prenatal steroids), the inclusion of patients with hydrocephalus, and the risk of necrotising enterocolitis or bowel perforation associated with indomethacin use. These confounding factors may heavily affect the conclusions of the study.

Implications of the study
The authors suggested that their findings may be useful in those neonatal intensive care units which accurately record the incidence of PDA in infants treated with indomethacin. These conclusions should be interpreted with caution given the limitations of the analysis highlighted.

Source of funding
None stated.

Bibliographic details

PubMedID
11847937

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Inflammatory Agents, Non-Steroidal /economics /therapeutic use; Cerebral Hemorrhage /economics /prevention & control; Cohort Studies; Cost-Benefit Analysis; Decision Trees; Ductus Arteriosus, Patent /economics /prevention & control; Humans; Indomethacin /economics /therapeutic use; Infant, Newborn; Infant, Very Low Birth Weight; MEDLINE; Randomized Controlled Trials as Topic; Retrospective Studies; Sensitivity and Specificity

AccessionNumber
22002000400

Date bibliographic record published
30/04/2003

Date abstract record published
30/04/2003