Dexamethasone is a cost-effective alternative to ondansetron in preventing PONV after paediatric strabismus repair


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 intervention health technologies were the use of prophylactic ondansetron and dexamethasone in the prevention of postoperative nausea and vomiting (PONV) in children undergoing strabismus repair.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population consisted of ASA physical status I or II children between the ages of 2 and 15 years who were undergoing strabismus repair under general anaesthesia. The study excluded children who had received drugs with antiemetic effects (e.g. phenothiazines, benzamides, scopolamine, corticosteroids, and tricyclic antidepressants) in the 24 hours before surgery.

Setting
The study setting was hospital. The economic analysis appears to have been carried out in New Delhi, India.

Dates to which data relate
No dates were specified for the effectiveness, resource use, or price data.

Source of effectiveness data
The evidence for the final outcomes was based on a single study.

Link between effectiveness and cost data
Costing appears to have been conducted prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were used to determine the sample size (power analysis before the study showed that 41 children would be required in each group to have a 95% chance (beta=0.05) of detecting a 50% relative reduction in PONV, from the study institute’s basal incidence of 80% with a type-I error of 5% (alpha=0.05) and 95% confidence interval limits). The study sample consisted of 135 children (age 2-15 years, ASA 1-11). After induction with halothane and nitrous oxide in oxygen or i.v. thiopental, the children received i.v. dexamethasone 1 mg/kg to a maximum of 25 mg.
ondansetron 100 micro g/kg to a maximum of 4 mg or placebo (n=45 for each study group). The mean (SD) age of children in the dexamethasone group was 7.6 (3.8) years as compared with 6.9 (3.5) years in the ondansetron group, and 7.11 (2.91) years in the placebo group.

Study design
The study was a randomized, placebo-controlled, double-blinded trial carried out in a single centre. The duration of follow-up appears to have been until discharge with no loss to follow-up. The study sample did not consume milk or solid food for at least 6 hours before operation: clear fluids were allowed until 3 hours before induction. The study did not control the volume of fluid children ingested in the 3 hours before surgery. A random number generator was used to assign each child prospectively to receive dexamethasone, ondansetron or saline placebo. An anaesthetist, not otherwise involved in patient care, prepared the study drugs to a fixed volume of 5 ml, to maintain the double-blind nature of the study. Intraoperative i.v. fluid management consisted of administration of lactated Ringer’s solution sufficient to correct half of the preoperative fluid deficit in the first hour, followed by maintenance fluids according to body weight. After operation, all children were transported to the post-anaesthesia care unit (PACU). The anaesthetist who provided intraoperative care assessed post-anaesthetic recovery using the modified Aldrete scoring system. Time to achieve complete recovery (score 10) was recorded for all children. The criteria for discharge from PACU to ward included stable vital signs, adequate pain control, and no nausea and vomiting in the first 2 hours after surgery. Children who had PONV and pain in the first 2 hours of stay were observed in PACU until they had remained free of PONV and pain for an hour.

Analysis of effectiveness
The principle used in the analysis of effectiveness appears to have been intention to treat. The PACU and ward nursing staff, who were aware of the nature of the study but blinded to the study drug, recorded episodes of PONV for the first 24 hours after the operation. A numeric scoring system for PONV was used (0 = no nausea or vomiting, 1 = nausea but no vomiting, 2 = vomiting once in 30 minutes or more, 3 = persistent nausea (longer than 30 min) or two or more vomits in 30 minutes). In this trial, the authors used parental assessment scores of the child's perioperative experience, duration of PACU stay, and fast tracking time as true outcome measures. Any child having a PONV score of 3 was considered to have severe PONV and was treated with metoclopramide 150 micro g/kg i.v. as a rescue antiemetic. The time to achieve eligibility for fast tracking (fast tracking time, FTT) was calculated as the time from the discontinuation of anaesthesia to the time at which the child had a patent airway without support, no PONV, no pain and a recovery score of 10. At the end of 24 hours after surgery, the primary caretaker was asked to give a global assessment of their satisfaction over the entire postoperative experience of the child (parental satisfaction score) using an 11-point verbal numeric scoring system (0 = not at all satisfied, 10 = fully satisfied). Side-effects were also recorded. The study groups were comparable in terms of baseline demographic and prognostic characteristics.

Effectiveness results
The effectiveness results were as follows:

The incidence and severity of PONV in the first 24 hours were significantly less in the dexamethasone and ondansetron groups than in the placebo group (p<0.05).

The incidence (p=0.04) and severity (p=0.03) of PONV at the 6-24 hour epoch were significantly less in the dexamethasone group than in the ondansetron group. The incidence of PONV was 33.3% in the ondansetron group, 24.4% in the dexamethasone group and 75.6% in the placebo group.

Recovery time (p=0.07), fast tracking time (p=0.6), and parental satisfaction scores (p=0.08) were comparable in both the ondansetron and the dexamethasone group.

Ondansetron and dexamethasone were statistically comparable for true, therapeutic outcome measures and side-effects.

Ondansetron and dexamethasone groups had significantly higher parental satisfaction scores than the placebo group, (p<0.0001).
Both FIT and PACU stays were significantly longer in the placebo group than in the ondansetron, (p=0.0003 and p=0.0002 respectively) and dexamethasone groups, (p=0.0068 and p=0.0074).

**Clinical conclusions**
Dexamethasone is as effective as ondansetron in decreasing the incidence and severity of PONV in the first 24 hours after operation. The antiemetic efficacy of dexamethasone is most pronounced in the late postoperative period. The incidence and severity of PONV in the late postoperative period are significantly lower in the dexamethasone group than in the ondansetron and placebo groups. This prolonged antiemetic efficacy of dexamethasone may be explained by its prolonged biological half-life (36-72 hours). The antiemetic and analgesic effects of dexamethasone were found to be more pronounced in the late postoperative period. This probably added to the comfort of the patients when they were discharged home. Dexamethasone is as effective as ondansetron in improving true outcome measures in this group of patients.

**Measure of benefits used in the economic analysis**
The benefit measure appears to be the positive number needed to prevent (NNTP) PONV (which indicates how many children had to be exposed to dexamethasone or ondansetron to prevent PONV), which was calculated as the reciprocal of the absolute risk reduction of the incidences of PONV from the basal (placebo) incidence for children who received dexamethasone or ondansetron.

**Direct costs**
Costs were not discounted due to the short time frame of the cost analysis. Some resource use items were reported separately from the costs. The cost analysis covered the acquisition cost of drugs per patient. The perspective adopted in the cost analysis was not explicitly specified. The price year was not given.

**Statistical analysis of costs**
No statistical analysis was performed on the cost outcomes. Two-sample t-tests and Mann-Whitney U-tests were used to compare PACU stay, perioperative fluid and analgesic requirements.

**Indirect Costs**
Indirect costs were not included.

**Currency**
US dollars ($). A conversion to Euros was also conducted.

**Sensitivity analysis**
No sensitivity analysis was conducted.

**Estimated benefits used in the economic analysis**
The positive NNTP was comparable in the ondansetron (NNTP = 2.36) and dexamethasone (NNTP =1.95) groups.

**Cost results**
The drug acquisition cost per patient was $0.47 (0.50 Euros) in the dexamethasone group and $8.72 (9.26 Euros) in the ondansetron group.

**Synthesis of costs and benefits**
The cost to benefit per patient (NNTP times the institutional drug acquisition cost) was 22.4 times higher in the ondansetron group than in the dexamethasone group.

Authors' conclusions
The cost to benefit a patient (i.e. NNTP times the cost of drug per patient) was 22 times higher in the ondansetron group than in the dexamethasone group. This reasserts the value of prophylactic dexamethasone as a cost-effective alternative to ondansetron.

CRDCOMMENTARY - Selection of comparators
The strategy of using placebo allowed the active value of the drug strategies to be evaluated. The authors justified this choice.

Validity of estimate of measure of effectiveness
The internal validity of the effectiveness results is likely to be high due to the randomised nature of the study design, power analysis being used to calculate the number of patients required in each group, and the comparability of the study groups in terms of the baseline characteristics. In this trial, the groups were comparable with respect to patient characteristics, surgical procedure, anaesthetics administered and i.v. fluids used in the perioperative period. Therefore, the difference in the incidence and severity of PONV and true and therapeutic outcome measures among the groups in this trial may reasonably be attributed to the study antiemetics that were administered. However, it was acknowledged that the study sample size was inadequate to identify an adverse effect with an incidence of less than 2.2% (100/45). The study sample appears to have been representative of the study population. No dates were given for the effectiveness data collection, which may adversely affect the generalisability of the effectiveness analysis.

Validity of estimate of measure of benefit
The estimate of the benefit measure was directly obtained from the effectiveness analysis. The choice of the benefit measure appears to be justified, although no explanation was given as to why no utility measure was adopted in the light of satisfaction being one of the outcome measures included in the study. Future studies in this area should consider this method.

Validity of estimate of costs
The cost analysis was rather brief and future studies should undertake more robust cost-analyses. The perspective adopted in the cost analysis was not stated and nor was the price year. Statistical analysis was not performed on the cost outcomes, although it was conducted on some of the resource use data. These features tend to limit the generalisability of the cost results.

Other issues
Despite the strength of the effectiveness part of the study, the study results may need to be treated with some degree of caution with respect to the limitations surrounding the cost analysis. The issue of generalisability to other settings or countries was not addressed, but some comparisons were made with other studies. The question of whether the study sample was representative of the study population was not discussed in the authors' comments. A cost-utility approach may also have been useful in the context in question.

Implications of the study
It was suggested that the timing of prophylactic antiemetic administration is important. The authors administered the drugs at the beginning of the procedure. It has been confirmed recently that dexamethasone is more effective when administered at induction than when given at the end of anaesthesia. Though it has been suggested that ondansetron given at the end of surgery will reduce antiemetic requirements more effectively in the postoperative period. In short surgical procedures like strabismus surgery, administering ondansetron at the beginning or end of surgery did not affect
the outcome. Furthermore, it was suggested that as the study was not adequately powered to identify an adverse effect with an incidence of less than 2.2% (100/45), meta-analysis may be effective in identifying adverse effects with low incidence. However, it was reported that a recent meta-analysis on dexamethasone and PONV did not reveal any significant side-effects. As yet, there is no evidence in the literature for dexamethasone’s potential side-effects, such as hyperglycaemia, delayed wound healing and hypothalamic pituitary adrenal axis suppression after a single dose.

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Other publications of related interest

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