Prevention of vomiting after paediatric strabismus surgery: a systematic review using the numbers-needed-to-treat method

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Summary
Randomized controlled studies were reviewed to assess the effectiveness and safety of antiemetics used for prophylaxis in paediatric strabismus surgery. Early and late vomiting (6 and 48 h after operation, respectively), and adverse effects were evaluated using the numbers-needed-to-treat method. In 27 reports with information on 2033 children, the mean incidence of early vomiting was 54 % and of late vomiting 59 %, without prophylaxis. Only three drugs were studied sufficiently for firm conclusions to be drawn. In the best documented regimen (droperidol 75 μg kg⁻¹), four children have to be given the drug to prevent one vomiting; of the three others, one may vomit and two would not have vomited anyway; fewer than one child in 100 may have an extrapyramidal reaction and 16 may have minor adverse effects. Metoclopramide 0.15 and 0.25 μg kg⁻¹ was significantly better than control only for early vomiting. Propofol had a high incidence of oculocardiac reflex without conferring any significant antiemetic effect: it should not be used. The benefits of prophylactic antiemetic therapy are not proven. (Br. J. Anaesth. 1995; 75:556–561)

Key words

Nausea and vomiting are common and unpleasant postoperative complications. There are many different approaches to prevent postoperative vomiting [1–6]. Despite this, neither the relative potency of antiemetics nor dose–response relationships have been established. Too few patients are examined in single studies to produce valid incidence data for adverse effects.

In this systematic review, we have compared the effectiveness and incidence of adverse effects of pharmacological interventions to prevent vomiting after paediatric strabismus surgery using odds ratio and number-needed-to-treat methods [7]. The odds ratio indicates how much more likely an individual given a particular treatment is to have a specific outcome than someone who is not given the treatment. The number-needed-to-treat indicates how many patients have to be treated in order to prevent one from having a specific outcome. It is used to produce clinically interpretable measures of benefit, minor harm and major harm. The clinical setting was chosen because of the high risk of vomiting [8, 9].

Methods
We included randomized controlled trials (RCT) which investigated the pharmacological prevention of vomiting after paediatric strabismus surgery, but not unpublished studies or abstracts. Studies with no definable placebo or no-treatment control group were not analysed, nor were data from post hoc analysis [10]. Nausea was not analysed if data from retching and vomiting were available from the same study [10]. Although not a classic antiemetic drug, propofol was included because it is thought to be antiemetic [11].

Medline was searched (January 1966 to December 1994) using the keywords “strabismus” and “vomiting”. Additional reports were identified from the reference lists of retrieved studies and from review articles. Each report which could possibly be described as an RCT was read independently by each of the authors, who scored the reports for quality using a three-item scale [12]. Non-randomized trials, and those where randomization was inadequate (alternate design, for instance) were excluded.

Information on the number and age of patients, in- or outpatient, dose, route and time of administration of antiemetics, anaesthetic techniques, definition of emesis (nausea, retching, vomiting) and adverse effects was obtained from each report. The incidence of early (up to 6 h after operation) and late (up to 48 h after operation) vomiting was recorded. If cumulative numbers of vomiting patients were not stated at these times, the earliest available vomiting incidence was considered as early vomiting [13].

Absence of vomiting was used as the index of effectiveness. Adverse effects were used, as defined in the original reports. The incidence of extrapyramidal symptoms was analysed only when described specifically. No weighting was made between

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different indices such as number of vomiting episodes, number of patients needing antiemetic rescue therapy or delay until discharge after surgery. The incidence of the oculocardiac reflex was used, as indicated in the different reports.

Odds ratios with 95% confidence intervals (CI) were calculated using a fixed effects model. Numbers-needed-to-treat and 95% confidence intervals were calculated [14]. This was done for effectiveness and adverse effects, both for individual reports and by combining single treatment or control arms. Calculations were performed using Excel V 4.0 on a Macintosh IIci.

Results

Thirty-three publications were identified, 27 by Medline and six from reference lists. Five of these six were identifiable retrospectively by Medline using a different search strategy. Six studies were excluded, two because of inadequate randomization [15, 16], one because of use of a historical control group [17] and three because they included various types of ophthalmic surgery in children and adults [18–20].

Twenty-seven studies (23 in English, three in German and one in French) were considered eligible, with information on 2033 children. Ten studies were placebo-controlled [21–30] and five had a no-treatment control [31–35]. Seven studies had other controls: in three of these a control group was not specified but could be defined for the purposes of this review [36–38]; in three this was not possible and they were excluded from the analysis [39–41]; one study had a non-antiemetic control [42]. Six studies with propofol were included [10, 13, 32, 43–45]. Tables containing the information extracted from these studies are available from the authors.

From the 24 studies, 38 treatment arms were analysed. The drugs were from eight different classes: butyrophenone (droperidol), metoclopramide, anticholinergics (atropine, hyoscine), phenothiazine (dixyrazine), 5-HT3 antagonist (ondansetron), benzodiazepine (lorazepam), lignocaine and propofol. Scopolamine patch (hyoscine), applied the evening before surgery, was used in one study [34]. All other treatments were given i.v. before, during or at the end of surgery.

Early vomiting occurred in 55% (range 18–88%) of 341 children in placebo control groups in 10 studies and in 50% (47–55%) of 50 children in no-treatment control groups in two studies. There was no significant difference between these rates of vomiting (odds ratio 0.81, 95% CI 0.45–1.48). The combined rate of early vomiting in placebo and no-treatment groups was 54%.

Late vomiting occurred in 64% (43–97%) of 138 children in placebo control groups in four studies and in 55% (45–69%) of 153 children in no-treatment control groups in five studies. There was no significant difference between these rates of vomiting (odds ratio 0.67, 95% CI 0.42–1.07). The combined rate of late vomiting in placebo and no-treatment control groups was 59%.

The best documented treatments, each with more than 100 patients, were droperidol, metoclopramide and propofol (tables 1, 2). Adverse effects were documented for propofol and droperidol 75 μg kg⁻¹ (table 3). No adverse effects were reported for lower doses of droperidol or for the other drugs used, except dixyrazine 0.25 mg kg⁻¹.

There appeared to be a dose–response relationship for droperidol 10–75 mg kg⁻¹ to prevent early and late vomiting (table 1). Only for droperidol 75 μg kg⁻¹ for early and late vomiting were the lower 95% CI of the odds ratio greater than 1.0, indicating a significant difference from controls for more than 200 children in 10 studies. At this dose the number-needed-to-treat for early vomiting was 3.5 (95% CI 2.8–4.8) and for late vomiting 4.4 (3.1–7.1). At this highest dose, one study reported spontaneously resolving extrapyramidal symptoms in two children and four studies reported explicitly the absence of extrapyramidal symptoms (table 3). Minor adverse effects such as postoperative sedation, drowsiness, restlessness and agitation were reported in several studies with droperidol 75 μg kg⁻¹ (table 3), and had a number-needed-to-treat of 6.3 (4.6–10.2) to produce one adverse effect.

Metoclopramide 0.10–0.25 mg kg⁻¹ appeared to show dose-dependent effectiveness in preventing early but not late vomiting (table 1). For early vomiting, with metoclopramide doses of 0.15 and 0.25 mg kg⁻¹, the lower 95% CI of the odds ratio were greater than 1.0, indicating significant improvement over control. This result was obtained with data which included one study with both doses which had a very high (88%) rate of early vomiting in the control group. Numbers-needed-to-treat to prevent early vomiting were 4.0 (2.7–7.6) and 2.5 (1.8–4.3) for 0.15 and 0.25 mg kg⁻¹, respectively. Information on late vomiting was available in only one study for each dose.

Numbers-needed-to-treat to prevent early and late vomiting with propofol compared with a halogenated inhalation anaesthetic were higher than with most antiemetics (table 2). With propofol-nitrous oxide, the lower 95% CI of the odds ratio for early vomiting was 1.0, indicating a result not significantly different from halogenated-nitrous oxide anaesthetics in 118 patients studied in five studies. For late vomiting the odds ratio indicated that propofol-nitrous oxide produced significantly less vomiting than halogenated–nitrous oxide anaesthesia with a number-needed-to-treat to prevent vomiting of 5.5, but with wide confidence intervals (3.4–15.1). Four studies reported a significantly higher incidence of the oculocardiac reflex in propofol-treated groups than in children given halogenated anaesthetics (Table 3), with a number-needed-to-treat of 3.6 (2.6–6.3).

Numbers-needed-to-treat to prevent vomiting were calculated for the other treatments (tables 1, 2). However, the results were based on small numbers of patients; only two reports with 78 patients for dixyrazine, two studies with 80 patients for propofol-nitrous oxide interactions and one report with about 50 patients for lorazepam or at most 30 patients each for ondansetron, lignocaine, hyoscine and atropine.
### Table 1

Numbers-needed-to-treat (NNT) to prevent early and late vomiting with droperidol, metoclopramide, dixyrazine, ondansetron, lignocaine, hyoscine, atropine, and lorazepam.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Absence of early vomiting</th>
<th>Absence of late vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Active</td>
<td>Control</td>
</tr>
<tr>
<td>Droperidol</td>
<td>10 µg kg⁻¹</td>
<td>23/26</td>
<td>23/28</td>
</tr>
<tr>
<td></td>
<td>20 µg kg⁻¹</td>
<td>22/34</td>
<td>16/33</td>
</tr>
<tr>
<td></td>
<td>50 µg kg⁻¹</td>
<td>30/57</td>
<td>24/57</td>
</tr>
<tr>
<td></td>
<td>75 µg kg⁻¹</td>
<td>20/269</td>
<td>131/277</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>0.10 mg kg⁻¹</td>
<td>24/25</td>
<td>23/28</td>
</tr>
<tr>
<td></td>
<td>0.15 mg kg⁻¹</td>
<td>69/120</td>
<td>40/124</td>
</tr>
<tr>
<td></td>
<td>0.25 mg kg⁻¹</td>
<td>42/58</td>
<td>18/56</td>
</tr>
<tr>
<td>Dixyrazine</td>
<td>0.25 mg kg⁻¹</td>
<td>17/20</td>
<td>9/20</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>0.15 mg kg⁻¹</td>
<td>27/30</td>
<td>15/30</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>2 mg kg⁻¹</td>
<td>20/25</td>
<td>12/25</td>
</tr>
<tr>
<td>Scopolamine TTS (hyoscine)</td>
<td>0.375–0.75 mg</td>
<td>21/25</td>
<td>13/25</td>
</tr>
<tr>
<td>Atropine</td>
<td>10 µg kg⁻¹</td>
<td>2025</td>
<td>19/25</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>10 µg kg⁻¹</td>
<td>34/43</td>
<td>31/43</td>
</tr>
</tbody>
</table>

### Table 2

Numbers-needed-to-treat (NNT) to prevent early and late vomiting with propofol. N₂O = Nitrous oxide; ∞ = Infinite value

<table>
<thead>
<tr>
<th>Absence of early vomiting</th>
<th>Absence of late vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>Control</td>
</tr>
<tr>
<td>Propofol–N₂O—Halogenated–N₂O controlled</td>
<td>Propofol–N₂O Halogenated–N₂O</td>
</tr>
<tr>
<td>Propofol–N₂O—Halogenated–N₂O controlled</td>
<td>Propofol–air–O₂ Halogenated–N₂O</td>
</tr>
<tr>
<td>Propofol without N₂O—Propofol–N₂O controlled</td>
<td>Propofol–air–O₂ Propofol–N₂O</td>
</tr>
</tbody>
</table>
Table 3 Numbers-needed-to-treat (NNT) for presence of drug-related adverse effects. Oculocardiac reflex = decrease in heart rate > 15–20 %. Minor adverse effects = sedation, drowsiness, restlessness, agitation

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio (95 % CI)</th>
<th>NNT (95 % CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Propofol—oculocardiac reflex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol—Halogenated</td>
<td>75/153 20/93</td>
<td>3.2 (1.9, 5.4)</td>
<td>3.6 (2.6, 6.3)</td>
</tr>
<tr>
<td>Droperidol 75 μg kg⁻¹—extrapyramidal symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Droperidol—Control</td>
<td>2/246 0/145</td>
<td>4.9 (0.3, 87.1)</td>
<td>123</td>
</tr>
<tr>
<td>Droperidol 75 μg kg⁻¹—minor adverse effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Droperidol—Control</td>
<td>81/311 22/248</td>
<td>3.1 (1.9, 4.9)</td>
<td>6.3 (4.6, 10.2)</td>
</tr>
</tbody>
</table>

Discussion

The high incidence of vomiting after strabismus surgery (mean 54 % for early vomiting and 59 % for late vomiting in control groups) is a particular problem because many of these procedures are performed as day-cases and vomiting can occur as late as 40 h after operation [34]. In one study of more than 300 outpatients undergoing strabismus surgery, 38 % of overnight admissions resulted from vomiting [46]. Conclusive comparative information is lacking on effectiveness and adverse effects of the various prophylactic treatments.

Combining the results of small studies increases the power, and the ability to produce meaningful results. This is particularly important in this circumstance, where rates of vomiting varied widely. The numbers-needed-to-treat method provides a clinically useful output, both for effectiveness and adverse effects [14]. Because about 50 % of children do not vomit even without antiemetic prophylaxis, the best number-needed-to-treat for effectiveness that could be obtained is about 2.

Evaluating the benefit of any treatment involves making comparisons. With the exception of propofol, treatments were compared with either placebo or no-treatment controls. While randomization controls selection bias, the lack of blinding inherent in a no-treatment control implies the possibility of observer bias. That no significant difference was seen between placebo and no-treatment groups for early or late vomiting suggested that the effect of any observer bias was limited. Because placebo and no-treatment controls were similar, analysis of treatments was not differentiated by type of control used.

No conclusions should be drawn about treatments which have been studied in fewer than 100 patients, which is the case for most treatments included here. While the results for dixyrazine and ondansetron appear to be good with numbers-needed-to-treat of about 2.5 to prevent late vomiting, the results were obtained from 78 and 30 patients, respectively; changes in just a few children vomiting or not vomiting in treatment or control groups would result in large changes in the number-needed-to-treat. Even where the odds ratios indicate a result significantly different from control, common sense indicates that these results should be treated with caution and at best be regarded as preliminary.

A similar warning should apply to the apparent dose-response relationships for droperidol and metoclopramide, although they are interesting because examples of dose-responses in humans are comparatively rare. The number of children studied at the lowest doses was small and the confidence intervals were wide; nevertheless there would seem to be sufficient information to suggest that the use of submaximal doses is not worthwhile.

For droperidol 75 μg kg⁻¹, about four children have to be given the drug to prevent one vomiting; of the other three, one may vomit and two would not have vomited anyway. It is an interesting judgement as to whether prophylaxis is worthwhile. Adverse effects and cost are the other factors in this argument. At the optimal dose of droperidol (75 μg kg⁻¹) extrapyramidal symptoms could be expected in fewer than 1 % of children. Adverse effects were reported sparsely for most other antiemetics. The dilemma then is whether no report means no adverse effect. No extrapyramidal effects occurred with metoclopramide, but the numbers studied were not large.

Propofol caused a surprisingly high incidence of the oculocardiac reflex despite anticholinergics (number-needed-to-treat 3.6). The oculocardiac reflex, also called trigeminal–vagal, usually produces bradycardia, but occasionally chaotic arrhythmia or sinoatrial arrest. It is caused by traction on the extraocular muscles. Serious complications may result [47]. It is managed by stopping traction and by giving anticholinergics. In view of this risk, and its poor effectiveness, propofol should not be considered as worthwhile prophylaxis.

Preventing vomiting in these children is clearly desirable and would also reduce enforced overnight stay and re-admission. What is striking is that rates of vomiting in the control groups varied widely across the studies, but the difficulties in conducting vomiting studies have already been emphasized [48]. Postoperative vomiting has many causes. At what point is prophylaxis a sledgehammer used to crack a nut? If on average 50 % of children vomit without treatment, and the best studied regimen prevents vomiting in 75 %, then the real “yield” is 25 %. This begs the question as to whether it would be better to wait and see who vomits and then treat. This is the pragmatic question that needs to be answered and perhaps defines the research agenda.
Acknowledgements
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