Randomized, double-blind study comparing the efficacy of moderate-dose metoclopramide and ondansetron for the prophylactic control of postoperative vomiting in children after tonsillectomy

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Background. Postoperative vomiting (POV) is a major cause of morbidity after tonsillectomy in children. It has been well established that anti-serotonergic agents are effective for the prophylactic control of POV in this patient group. It has been suggested that at moderate doses (0.5 mg kg\(^{-1}\)), metoclopramide is also an effective agent. No study has been performed comparing the efficacy of an anti-serotonergic agent and moderate-dose metoclopramide.

Methods. A total of 557 children undergoing tonsillectomy with or without adenoidectomy were randomly allocated to receive either ondansetron 0.1 mg kg\(^{-1}\) or metoclopramide 0.5 mg kg\(^{-1}\). All received a standardized muscle-relaxant anaesthetic and dexamethasone 0.1 mg kg\(^{-1}\). The primary outcome was any vomit in the immediate postoperative period. Comparisons were made of the proportion in each group reaching the primary outcome and the time until their first vomit. The study was designed to detect equivalence.

Results. The incidence of vomiting in the group receiving ondansetron (25.3%) was 12% lower (95% CI 4.4–19.7) than those in metoclopramide (37.3%). The time until first vomit was significantly longer in the group receiving ondansetron (hazard ratio 0.61, 95% CI 0.45–0.82).

Conclusions. Although the incidence of vomiting was similar, when these results are compared with a pre-specified zone of equivalence of 0–15%, it cannot be concluded that the effect of metoclopramide is equivalent to ondansetron. Survival analysis indicated that those in the metoclopramide group vomited substantially earlier. It is concluded, therefore, that ondansetron 0.1 mg kg\(^{-1}\) is a superior drug to metoclopramide 0.5 mg kg\(^{-1}\) for the prophylactic control of POV in children undergoing tonsillectomy.

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A systematic review and meta-analysis of drugs and techniques used to prophylactically reduce the incidence of postoperative vomiting (POV) in children after tonsillectomy indicated that the serotonergic agents are extremely effective compared with placebo (pooled OR 0.12, 95% CI 0.07–0.20).\(^1\) In the same analysis, metoclopramide was also identified as being an effective agent (OR vs placebo 0.51, 95% CI 0.34–0.77). Because only placebo-controlled studies were included in the meta-analysis, the relative efficacy of these two drugs could not be accurately quantified.
Metoclopramide is a dopamine antagonist that has been widely used as an anti-emetic in both children and adults. Its anti-emetic effects result from antagonism of dopamine receptors in the central nervous system (specifically the chemoreceptor trigger zone) and its selective peripheral cholinergic stimulant effects of the proximal gastrointestinal tract. Traditionally, doses of 0.1 mg kg \(^{-1}\) have been used in children, with the total dose not exceeding 0.5 mg kg \(^{-1}\) per day. It has been reported, however, that at higher doses than these, metoclopramide has anti-serotonergic actions and hence possibly greater clinical efficacy. 

It is a standard clinical practice at the Royal Children’s Hospital (RCH), Melbourne, Australia, to administer metoclopramide 0.5 mg kg \(^{-1}\) i.v. intraoperatively for the prophylactic control of postoperative nausea and vomiting. The safety of these higher doses is based on clinical experience over a 15 yr period and reports of the use of similar and even higher doses in paediatric oncology. The clinical impression of the anaesthetists at RCH is that this ‘moderate-dose’ of metoclopramide (0.5 mg kg \(^{-1}\)) is more effective than metoclopramide (0.1 mg kg \(^{-1}\)) in children undergoing tonsillectomy and possibly as effective as ondansetron.

Anti-serotonergic agents are currently the prophylactic anti-emetic agent of choice in this patient group but are substantially more expensive than metoclopramide. This study was designed to investigate whether moderate-dose metoclopramide was as effective as ondansetron for the prophylactic control of POV in children after tonsillectomy.

### Methods

After approval from the institutional ethics committee, a double-blind, randomized, study was conducted between October 1999 and March 2004. Patients aged between 6 months and 12 yr old with an ASA rating of I–III undergoing inpatient tonsillectomy with or without adenoidectomy were eligible. Patients were excluded if they had severe obstructive sleep apnoea, clinically significant cardiac, respiratory, hepatic, or renal disease, had participated in another clinical trial in the last month, or had a documented allergy to any of the specified study drugs. Written informed consent was obtained according to the requirements of the institution’s ethics committee.

Participants were block randomized to receive either ondansetron 0.1 mg kg \(^{-1}\) (maximum dose 8 mg) or metoclopramide 0.5 mg kg \(^{-1}\). Ondansetron 0.1 mg kg \(^{-1}\) was used after the recommendations of the authors of a pharmacokinetic evaluation of ondansetron in children undergoing ENT surgery. This dose is consistent with current clinical practice at RCH and was therefore acceptable to all anaesthetists. The dose of metoclopramide selected for this trial was based on the practice and clinical impression of anaesthetists at RCH. It is believed that at these doses, metoclopramide may have anti-serotonergic effects.

Patients were allocated according to a master sheet, by a member of the study team not involved in the clinical component of the study. Neither participants nor the staff involved in the assessment of patients was aware of the treatment group allocations.

All participants received a standardized muscle-relaxant general anaesthetic. Oral acetaminophen 20–30 mg kg \(^{-1}\) was given 30 min before induction of anaesthesia. Anaesthesia was induced using propofol 2–4 mg kg \(^{-1}\), or sevoflurane, and maintained using nitrous oxide, isoflurane, morphine 0.05–0.1 mg kg \(^{-1}\), and atracurium 0.3–0.5 mg kg \(^{-1}\). All patients received dexamethasone 0.1 mg kg \(^{-1}\) and 20 ml kg \(^{-1}\) of Hartman’s solution i.v. Neuromuscular block was antagonized using neostigmine 0.05 mg kg \(^{-1}\) and atroипine 0.02 mg kg \(^{-1}\). Postoperative analgesia was provided using acetaminophen 20 mg kg \(^{-1}\) p.o. four hourly p.r.n. and codeine 0.5–1.0 mg kg \(^{-1}\) p.o. four hourly p.r.n. Any deviations from the above protocol were documented.

The study drugs were prepared either by a member of the research team not involved in the assessment of patients or by the RCH Pharmacy Department. Appropriate doses of the drugs according to the patient’s weight were diluted to 10 ml with normal saline in a 10 ml syringe. The syringe was labelled with the patient’s name, weight, and study number. The drug was administered at or immediately after induction.

The primary outcome used was any vomit before discharge from hospital. A vomit was defined as an active expulsive effort, with or without the ejection of gastric material. Information about vomiting was documented by the recovery room or ward nursing staff. The accuracy of documentation was checked by the research staff by interviewing parents, participants when appropriate, and nursing staff before discharge.

An initial sample size estimation was performed based on the assumption that the incidence of POV after tonsillectomy in children receiving ondansetron 0.1 mg kg \(^{-1}\) intraoperatively was 25% \(^{8-11}\). An incidence of vomiting of 40% in the metoclopramide group would be considered to be clinically worse, that the true incidence of vomiting with metoclopramide was 30%, \(\alpha=0.05, \beta=0.2,\) and that the study was designed to establish equivalence. On the basis of the above assumptions, the sample size calculation estimated that 284 participants were required in each group. Alternatively expressed, this would ensure that the two-sided 95% CI for the difference between the groups would extend only 7.5% from the observed difference. It was decided to recruit 300 patients per group to allow for protocol errors.

To allow the results of the study to be interpreted, a prespecified zone of clinical equivalence was established by asking 14 paediatric anaesthetists: ‘If the anti-emetic you used currently had an incidence of vomiting of 40%, how much better would a new drug have to be to induce you to change your practice and use the new drug?’ The concept...
Comparison of ondansetron and metoclopramide

of number-needed-to-treat (NNT) was outlined to aid them in their decision-making as was the fact that the ‘new’ drug would cost $17 extra per patient. The median of the 14 values given was 15%, that is, any improvement less than this would be considered to be insignificant in this clinical setting. The zone of clinical equivalence therefore was considered to be 0–15%.

The names of the drugs were not specified to avoid any emotive response to either of the two drugs, and a baseline incidence of 40% was chosen since this is the approximate incidence of POV when dexamethasone alone is prophylactically administered to children undergoing tonsillectomy.11 This was the appropriate baseline since dexamethasone is routinely used by all anaesthetists at RCH in this clinical setting and was to be included for all patients as part of the study protocol.

An unplanned interim analysis was performed after 2 yr due to a slower than expected recruitment rate. At this point, only 301 patients had been recruited and a more accurate estimation of the likely number of participants needed was required to allow adequate resource allocation. There was never any intention of concluding the study at this point. The results indicated that the incidences of POV associated with the use of ondansetron and metoclopramide were 26.8% and 34.2%, respectively. The absolute difference was 7.4% (95% CI −3.1% to 17.9%). These data confirmed the assumptions made in the original sample size calculation and hence the target remained unchanged at 284 per group.

The primary analysis calculated the absolute difference in the proportion of each group reaching the primary outcome together with a 95% CI. This was interpreted according to the pre-established zone of equivalence. An unadjusted OR was also calculated. Logistic regression was used to investigate the effect of the pre-specified covariates age, weight, gender, and concurrent adenoidectomy. Time until first vomit was also analysed using a median test and Cox’s proportional hazards model. All analyses were performed on an intention-to-treat basis.

Results

A total of 600 children were recruited and underwent randomization. Forty-three children subsequently had their surgery cancelled due to a lack of operating time, a shortage of hospital beds, or due to illness precluding safe anaesthesia. Therefore, 557 children were included in the final analysis. The groups were well matched for age, weight, sex, and the proportion having concurrent adenoidectomies (Table 1). The groups were also well matched for concomitant opioid administration and intraoperative complications. Twenty-seven of the withdrawals after recruitment were in the ondansetron group (9.0%), compared with 16 in the metoclopramide group (5.3%).

Table 1 Patients’ characteristics and other variables. *Mean (range) or mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Metoclopramide n=284</th>
<th>Ondansetron n=273</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)*</td>
<td>5.5 (1–12)</td>
<td>5.0 (2–12)</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>22.5 (9.5)</td>
<td>21.1 (8.5)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>42%</td>
<td>45%</td>
</tr>
<tr>
<td>Concurrent adenoidectomies</td>
<td>229 (81%)</td>
<td>232 (85%)</td>
</tr>
<tr>
<td>No. of participants with intraoperative complications (bleed &gt;60 ml, duration &gt;1 h, anaesthetic complication)</td>
<td>25 (8.8%)</td>
<td>26 (9.5%)</td>
</tr>
<tr>
<td>Opioid use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative morphine 0.05 mg kg(^{-1})</td>
<td>54</td>
<td>49</td>
</tr>
<tr>
<td>Intraoperative morphine 0.1 mg kg(^{-1})</td>
<td>214</td>
<td>203</td>
</tr>
<tr>
<td>Intraoperative fentanyl 2 µg kg(^{-1})</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Intraoperative fentanyl 3 µg kg(^{-1})</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Postoperative codeine (mg kg(^{-1}) per 24 h)*</td>
<td>1.7 (1.7)</td>
<td>1.4 (1.5)</td>
</tr>
<tr>
<td>No. of other protocol violations</td>
<td>10 (3.5%)</td>
<td>7 (2.6%)</td>
</tr>
<tr>
<td>No. of recruited but surgery then cancelled</td>
<td>27 (9%)</td>
<td>16 (5.3%)</td>
</tr>
</tbody>
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The point estimate for the difference in the proportion vomiting was 12.0%, with the upper limit of the 95% CI extending to 19.7% (Table 2). The OR adjusted for age, weight, gender, and concurrent adenoidectomy using logistic regression was 0.59 (95% CI 0.41–0.85), which did not differ substantively from the unadjusted estimate (Table 2).

Figure 1 shows the pattern of vomiting in each group over time. A difference in the time until first vomit was identified when survival analysis was performed using Cox’s proportional hazards [hazard ratio 0.61, 95% CI 0.45–0.82 with no evidence that any of the tested covariates (age, weight, sex, and the concurrent adenoidectomy) significantly affected the estimate].

Analysis of the 175 children who vomited indicated that the median time until first vomit was substantially shorter for those receiving metoclopramide compared with those receiving ondansetron (2.1 vs 6.5 h, respectively, P<0.002).

Anaesthetists were required to document the presence or absence of adverse events during anaesthesia. No such events were recorded for either group of patients. This was particularly of interest for metoclopramide due to the risk of extrapyramidal reactions (95% CI for metoclopramide 0–1.3%).

Discussion

In the first large randomized-controlled trial comparing ondansetron 0.1 mg kg\(^{-1}\) and metoclopramide 0.5 mg kg\(^{-1}\) for the prophylactic control of vomiting after tonsillectomy, we found a modest but clear advantage for ondansetron (absolute difference 12%, 95% CI 4.4–19.7). There was no evidence of confounding as a result of the patient’s age, gender, weight, or the performance of concurrent adenoidectomy.
Percentage reaching primary outcome (respectively) presented in a recent meta-analysis. The OR for metoclopramide compared with placebo was 0.21 (95% CI 0.08–0.54). This study also included a group that received ondansetron 0.15 mg kg$^{-1}$. The OR for the ondansetron group compared with placebo was 0.29 (95% CI 0.12–0.69), which was statistically indistinguishable from the metoclopramide group, although the group sizes were small. Further evidence of the similar efficacy of the two drugs at these doses is found in the summary ORs for metoclopramide and ondansetron compared with placebo [0.51 (95% CI 0.34–0.77) and 0.36 (95% CI 0.29–0.46), respectively] presented in a recent meta-analysis. The estimated OR (0.57, 95% CI 0.39–0.83) in the current study for difference in the incidence of vomiting is consistent with these results.

The NNT for the measured difference in this trial was 8.3. The RCH pharmacy estimated that for a single dose for a 20 kg patient, ondansetron cost approximately (AUS) $17.00 more than metoclopramide. This means that if ondansetron was used routinely for prophylaxis, the cost to prevent an additional person from vomiting would be approximately (AUS) $142.00. On the basis of the 95% CI, the true cost is likely to lie between (AUS) $86 and $386.00. This evidence of more frequent and earlier vomiting in the metoclopramide group may be explained by the pharmacokinetics of the drugs. Although the elimination half-lives of the two drugs are similar (2.5–6 h), it is possible that the effector-site concentration of metoclopramide at the dose used still decreases below the therapeutic threshold. This may suggest the need for a larger loading dose of metoclopramide or the need for re-administration of the drug. The use of larger doses has been reported in the literature in other patient groups, although these may be associated with a higher incidence of side-effects.

The use of metoclopramide in children has been limited by concerns about the increased incidence of extrapyramidal side-effects in this patient group. Whereas the incidence of extrapyramidal side-effects is approximately 0.2% in the adult population, it has been reported to be up to 25% in children. The use of metoclopramide, however, was based on its use and efficacy in other paediatric patient groups without undue side-effects. The dose of metoclopramide selected for this trial was based on the standard practice of anaesthetists at RCH and the fact that it has been reported that at these doses, metoclopramide has anti-serotinergic effects thus perhaps accounting for additional anti-emetic activity. The use of even larger doses of metoclopramide in children has been reported to be common practice in the oncology literature without unacceptable levels of side-effects.

All patients in this study were paralysed making the diagnosis of extrapyramidal reactions difficult and hence could explain the absence of any observed reactions. Paralysis, however, lasted for <1 h and untreated extrapyramidal reactions are said to last for several hours. It might be reasonable to expect, therefore, that a reaction would still be able to be detected.

The decision to use ondansetron 0.1 mg kg$^{-1}$ was made after the recommendations of the authors of a pharmacokinetic evaluation of ondansetron in children undergoing ENT surgery together with the fact that this dose was routinely used in clinical practice at RCH.

Not all children eligible for the trial were approached. This was due to the limited resources available to the research team and the fact that a research assistant was available only 3 out of 5 days each week to recruit. This situation was further complicated by the commencement of another funded project which drew upon the same patient pool. It is unlikely that this recruitment pattern created a significant generalizability problem for the trial.

Rescue therapy (ondansetron 0.1 mg kg$^{-1}$) was administered after either two vomits in the recovery room or...
one vomit on the ward. This made it impossible to assess the effect that a single prophylactic dose of either of the two study drugs had on the long-term pattern of vomiting. Interpretation of the results is therefore limited to the prevention of a single vomit.

The clinical importance of a single vomit has been questioned by some authors. This is a philosophical argument based on the premise that vomiting occurs so frequently that it should be considered a normal phenomenon of little clinical significance. The alternative argument is that vomiting and retching are extremely unpleasant experiences that most patients would prefer to avoid. This ‘desire to avoid’ has been quantified in a number of clinical studies. Hence, the importance of a single vomit due to its effect on patient satisfaction, a so-called ‘true’ outcome, can be easily defended.

Dexamethasone is routinely used by all anaesthetists at this institution and was consequently included in the anaesthetic protocol for this trial. It has been shown to have significant anti-emetic effects (RR=0.55, 95% CI 0.41–0.74). However, its inclusion does not confound the results since all patients received the same dose by weight.

An interim analysis was performed to assess the resources required to complete the trial. At no time was there any intention to conclude the trial on the basis of this analysis. As a result, no penalties were factored into the final analysis. In any event, the results of the interim analysis confirmed the appropriateness of the original sample size calculation and no alterations were made to the original protocol.

Forty-three children were consented and subsequently had their surgery cancelled. These cancellations were largely due to the need for premedication with midazolam. These patients were approximately equally distributed between the two groups. Variations in the use of opioids are documented in Table 1 and again were small and unlikely to have influenced the results.

In conclusion, the results suggest that metoclopramide 0.5 mg kg⁻¹ and ondansetron 0.1 mg kg⁻¹ in the presence of dexamethasone have a similar, but not equivalent, efficacy in the prevention of vomiting after tonsillectomy in children. Analysis of those who did vomit suggested that those receiving metoclopramide vomited earlier. This may have been indicative of declining effector-site concentrations and be able to be remedied with repeated dosing.

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