British Journal of Anaesthesia **97** (**5**): 593–604 (2006)
doi:10.1093/bja/ael256 Advance Access publication September 26, 2006

BJA

REVIEW ARTICLE

Prophylaxis of postoperative vomiting in children undergoing tonsillectomy: a systematic review and meta-analysis

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Postoperative vomiting (POV) remains one of the commonest causes of significant morbidity after tonsillectomy in children. A variety of prophylactic anti-emetic interventions have been reported, but there has only been a limited systematic review in this patient group. A systematic search was performed by using Cochrane Controlled Trials Register, MEDLINE and EMBASE to identify double-blind, randomized, placebo-controlled trials of prophylactic anti-emetic interventions in children undergoing tonsillectomy, with or without adenoidectomy. The outcome of interest was POV in the first 24 h. Summary estimates of the effect of each prophylactic anti-emetic strategy were derived using fixed effect meta-analysis. Where appropriate, dose–response effects were estimated using logistic regression and 22 articles were identified. Good evidence was found for the prophylactic anti-emetic effect of dexamethasone [odds ratio (OR) 0.23, 95% CI 0.16–0.33], and the serotinergic antagonists ondansetron (OR 0.36, 95% CI 0.29–0.46), granisetron (OR 0.11, 95% CI 0.06–0.19), tropisetron (OR 0.15, 95% CI 0.06–0.35) and dolasetron (OR 0.25, 95% CI 0.1–0.59). Metoclopramide was also found to be efficacious (OR 0.51, 95% CI 0.34–0.77). There is not sufficient evidence to suggest that dimenhydrinate, perphenazine or droperidol, in the doses studied, are efficacious, nor were gastric aspiration or acupuncture. In conclusion, dexamethasone and the anti-serotinergic agents appear to be the most effective agents for the prophylaxis for POV in children undergoing tonsillectomy.

Br J Anaesth 2006; **97**: 593–604

Keywords: anaesthesia, paediatric; meta-analysis; surgery, otolaryngeal; vomiting, anti-emetics

Tonsillectomy with or without adenoidectomy remains one of the most frequently performed paediatric surgical procedures worldwide.[58 62 91] Postoperative nausea and vomiting (PONV) is one of the most common, significant postoperative complications associated with this procedure.[8 36] Without prophylaxis, more than 70% of children undergoing tonsillectomy will experience at least one episode of vomiting in the postoperative period.[20 33 37 42] PONV has been reported to be the commonest cause of delayed discharge or overnight admission in day-case tonsillectomies.[2 62] It has also been reported to be associated with an increased risk of bleeding, aspiration of gastric contents, dehydration and electrolyte disturbance.[70]

A variety of different anti-emetic drugs and techniques have been described for the prophylactic control of PONV in this group. The aim of this study was to systematically review the currently available literature relating to interventions used to prophylactically reduce the incidence of postoperative vomiting (POV) in children after tonsillectomy, with or without adenoidectomy and where appropriate, perform a meta-analysis.

Methods

Searches of the Cochrane Controlled Trials Register (CCTR), MEDLINE and EMBASE were performed for the years 1966–September 2003. The search strategy used for the CCTR (Table 1) identified 49 potentially eligible studies. MEDLINE was also searched using the keywords such as child, tonsillectomy and POV. The search was re-run adding in each of the individual drugs or techniques to be reviewed (Table 2). In addition, the scientific abstracts of

Table 1 Search strategy for the CCTR

Subject headings
#1. Child
#2. Tonsillectomy
#3. Postoperative vomiting
#4. Postoperative nausea and vomiting explode all trees (MeSH)
#5. #3 or #4
#6. #1 and #2 and #5

Table 2 Drugs and techniques included in MEDLINE search

Drug or technique
Metoclopramide
Dimenhydrinate
Droperidol
Perphenazine
Ondansetron
Granisetron
Tropisetron
Dolasetron
Midazolam
Dexamethasone
Gastric aspiration
Acupuncture

meetings were reviewed in *Anesthesia and Analgesia*, *Anesthesiology* and the *British Journal of Anaesthesia*. Any other study included in the reference list of any of these publications but not already identified was also obtained. A further 43 studies were identified giving a total of 92 potentially eligible studies. Paper copies of each were retrieved for the final assessment of eligibility.

Eligible studies were restricted to randomized, double-blind, placebo-controlled trials available in English, that investigated the prophylactic reduction of POV in paediatric patients aged 18 yr or less, who had undergone tonsillectomy with or without adenoidectomy. Both pharmacological and non-pharmacological interventions were included. The outcome measure was POV in the first 24 h.

A systematic review and meta-analysis of papers investigating the anti-emetic effects of dexamethasone[5 10 57 60 82 97 103] had recently been published.[91] Two additional placebo-controlled studies of this intervention were identified[4 19] and hence the meta-analysis was re-performed to include these studies.

All studies were reviewed by two authors (C.M.B. and P.S.M.) and agreement was reached regarding eligibility. All trials satisfying the inclusion criteria were included in the initial analysis. A sensitivity analysis was then performed which excluded trials with methodological flaws such as a significant loss-to-follow-up,[33] inappropriate early termination[87] and those trials whose protocols varied significantly from other studies.[9 50 87] No other attempt was made to rank the selected studies according to their quality.

Analyses were conducted separately for each drug or intervention using Stata 8.1. For trials in which a drug was administered at more than one dose, the overall effect of the drug was derived by combining data from all groups receiving the drug. Fixed-effect summary odds ratios (ORs) for the effect of each drug on vomiting were derived using the Mantel–Haenszel method. The amount of between-trial heterogeneity was measured using the I^2 statistics[89] and heterogeneity was tested using the Q statistic. Evidence of publication and other bias was sought by plotting funnel plots according to the guidelines of Sterne and Egger[88] and using the regression test proposed by Egger and colleagues.[18]

Table 3 Numbers needed to treat to benefit one child, according to the percentage of children who vomit in the absence of medication, and the odds ratio (OR) for the effect of the anti-emetic intervention

Percentage vomiting	OR for the effect of anti-emetic intervention							
	0.9	**0.8**	**0.7**	**0.6**	**0.5**	**0.4**	**0.3**	**0.2**
30	46.2	22.4	14.4	10.5	8.1	6.5	5.4	4.5
35	42.4	20.4	13.1	9.5	7.3	5.8	4.7	4.0
40	40.0	19.2	12.2	8.8	6.7	5.3	4.3	3.5
45	38.6	18.4	11.6	8.3	6.3	4.9	4.0	3.2
50	38.0	18.0	11.3	8.0	6.0	4.7	3.7	3.0
55	38.2	18.0	11.2	7.9	5.9	4.5	3.5	2.8
60	39.2	18.3	11.4	7.9	5.8	4.4	3.5	2.7
65	41.1	19.1	11.8	8.1	5.9	4.5	3.4	2.6
70	44.3	20.5	12.5	8.6	6.2	4.6	3.5	2.6
75	49.3	22.7	13.8	9.3	6.7	4.9	3.6	2.7
80	57.5	26.3	15.8	10.6	7.5	5.4	3.9	2.8

Some trials had compared different doses of the same drug; therefore, standard methods for meta-analysis could not be used in analysis of dose–response effects. Instead, logistic regression was used to estimate dose–response effects of each drug in each trial. Logistic regression was also used to estimate the overall effect of each dose of each drug, across trials, by combining data across trials and including indicator variables for trials in the model. When there was evidence that the effect of a drug differed according to dose, logistic regression was used to estimate the summary OR per unit increase in dose, in each trial. These were then combined using fixed-effect meta-analysis. Table 3 has been included to allow ORs to be converted into NNT.

Results

Of the 92 studies reviewed, 22 met the inclusion criteria. Table 4 lists the characteristics of these studies. Individual study results and the results of the meta-analysis are given in Table 5. Excluded studies are listed in Appendix Table A1.

Pharmacological strategies

Metoclopramide

There were four studies[20 33 69 87] testing the efficacy of metoclopramide (Table 4). All used i.v. administration, and the same definition of vomiting, with one exception[87]

Table 4 Description of studies satisfying inclusion criteria. T's, tonsillectomy; A's, adenoidectomy; MRGA, muscle relaxant general anaesthetic; GA, general anaesthetic; ?, not specified; N/A, not applicable; ITT, intention-to-treat; ATP, according-to-protocol

Intervention	Dose (mg kg^{-1})	Route of administration	*n*	Primary author	Age (yr)	Type of surgery and technique	Anaesthetic details	Definition of POV	Use of postop. opioids?	Type of analysis
Metoclopromide	0.15	i.v.	102	Ferrari[20]	1–15	T's with or without A's	Non-standardized, non-MRGA	Vomit	?	ITT
	0.5	i.v.	239	Furst[33]	2–12	T's with or without A's	Non-standardized, non-MRGA	Vomit	No	ATP
	0.25, 0.5	i.v.	200	Rose and Martin[69]	2–12	T's with or without A's	Non-standardized, MRGA	Vomit	No	ATP
	0.25	i.v.	120	Stene[87]	2–12	T's with or without A's	Standardized MRGA	Retch or vomit	?	ATP
Dimenhydrinate	0.5	i.v.	74	Hamid[37]	2–10	T's with A's	Standardized MRGA	Retch or vomit	No	ATP
Droperidol	0.075	i.v.	239	Furst[33]	2–12	T's with or without A's	Non-standardized, non-MRGA	Vomit	No	ATP
Perphenazine	0.07	i.v.	258	Splinter and Roberts[84]	2–12	T's with or without A's	Non-standardized GA	Vomit	?	ATP
Ondansetron	0.15	i.v.	239	Furst[33]	2–12	T's with or without A's	Non-standardized, non-MRGA	Vomit	No	ATP
	0.15	i.v.	60	Litman[50]	>3	T's with or without A's	Standardized MRGA	?	No	ATP
	0.1	Oral	233	Splinter and Baxter[79]	2–14	T's with A's	Non-standardized MRGA	?	No	ITT
	0.15	Oral	136	Rose and Brenn[68]	1.5–12	T's with or without A's	Standardized MRGA	Vomit	No	ATP
	0.15, 0.3	i.v.	200	Rose and Martin[69]	2–12	T's with or without A's	Non-standardized MRGA	Vomit	No	ATP
	0.15	i.v.	120	Stene[87]	2–12	T's with or without A's	Standardized MRGA	Retch or vomit	?	ATP
	0.1	i.v.	427	Morton[53]	1–12	T's with or without A's	Non-standardized GA	Retch or vomit	No	ITT
	0.1	i.v.	71	Hamid[37]	2–10	T's with A's	Standardized MRGA	Retch or vomit	No	ATP
	0.1	i.v.	90	Barst and Leiderman[7]	1–18	T's with or without A's	Standardized MRGA	Retch or vomit	?	ATP
	0.15	i.v.	149	Sukhani[94]	2–12	T's with or without A's	Standardized MRGA	Retch or vomit	?	ATP
Granisetron	0.01	i.v.	54	Carnahan[9]	2–8	T's with A's	Standardized MRGA	?	?	ITT
	0.02, 0.04, 0.08	Oral	160	Fujii[27]	4–10	T's with or without A's	Standardized non-MRGA	Retch or vomit	No	ITT
	0.04	i.v.	120	Fujii[30]	4–10	T's with or without A's	Standardized MRGA	Retch or vomit	No	ITT
Tropisetron	0.1	i.v.	47	Ang[3]	2–12	T's with or without A's	Non-standardized MRGA	Retch or vomit	No	ATP
	0.2	i.v.	71	Jensen[42]	2–14	T's with or without A's	Non-standardized MRGA	Retch or vomit	No	ATP
Dolasetron	0.5	i.v.	149	Sukhani[94]		T's with or without A's	Standardized MRGA	Retch or vomit	?	ATP
Midazolam	0.075	i.v.	215	Splinter[80]	1.5–14	T's with or without A's	Non-standardized, MRGA	?	No	ITT
Gastric aspiration	–	N/A	74	Jones[43]	2–11	T's with or without A's	Standardized MRGA	Vomit	?	ATP
P6 acupoint stimulation	–	N/A	45	Yentis[107]	2–11	T's	Standardized MRGA	Retch or vomit	No	ITT
	–	N/A	100	Shenkman[75]	2–12	T's with or without A's	Standardized MRGA	Retch or vomit	No	ITT
	–	N/A	120	Rusy[71]	4–18	T's with or without A's	Standardized MRGA	Vomit	No	ATP

Table 5 Results of individual studies and of meta-analysis

Intervention	Primary author	Dose (mg kg^{-1})	No. who did not vomit	No. who did vomit	OR (95% CI)
Metoclopramide	Ferrari[20]	0	15	36	1 (ref.)
		0.15	27	24	0.37 (0.16–0.84)
	Furst[33]	0	23	38	1 (ref.)
		0.5	25	34	0.82 (0.4–1.71)
	Rose[69]	0	20	20	1 (ref.)
		0.25	24	16	0.67 (0.31–1.44)
		0.5	33	7	0.21 (0.08–0.54)
	Stene[87]	0	11	25	1 (ref.)
		0.25	19	22	0.51 (0.2–1.3)
Overall estimate (heterogeneity P=0.46, I^2=0%)					0.51 (0.34–0.77)
Sensitivity analysis					0.39 (0.22–0.68)
Dimenhydrinate	Hamid[37]	0	8	36	1 (ref.)
		0.5	5	19	0.84 (0.20–3.7)
Droperidol	Furst[33]	0	23	38	1 (ref.)
		0.075	22	36	0.99 (0.44–2.22)
Perphenazine	Splinter[84]	0	52	76	1 (ref.)
		0.07	75	55	0.5 (0.31–0.82)
Ondansetron	Furst[33]	0	23	38	1 (ref.)
		0.15	45	16	0.22 (0.1–0.46)
	Litman[50]	0	8	22	1 (ref.)
		0.15	23	7	0.11 (0.03–0.36)
	Splinter[79]	0	57	67	1 (ref.)
		0.1	66	43	0.55 (0.33–0.93)
	Rose[68]	0	28	17	1 (ref.)
		0.15	39	7	0.3 (0.11–0.81)
	Rose[69]	0	20	20	1 (ref.)
		0.15	31	9	0.29 (0.12–0.69)
		0.3	37	3	0.08 (0.02–0.28)
	Stene[87]	0	22	25	1 (ref.)
		0.15	32	11	0.3 (0.12–0.74)
	Morton[53]	0	100	115	1 (ref.)
		0.1	127	85	0.58 (0.4–0.85)
	Hamid[37]	0	8	36	1 (ref.)
		0.1	15	10	0.15 (0.05–0.45)
	Barst[7]	0	35	10	1 (ref.)
		0.1	42	3	0.25 (0.06–0.98)
	Sukhani[94]	0	46	54	1 (ref.)
		0.15	41	9	0.19 (0.08–0.43)
Overall estimate (heterogeneity P=0.013, I^2=57.2%)					0.36 (0.29–0.46)
Sensitivity analysis					0.41 (0.32–0.53)
Granisetron	Carnahan[9]	0	8	18	1 (ref.)
		0.01	23	5	0.1 (0.03–0.35)
	Fujii[25]	0	10	24	1 (ref.)
		0.02	19	21	0.46 (0.18–1.21)
		0.04	34	6	0.07 (0.02–0.23)
		0.08	36	4	0.05 (0.01–0.16)
	Fujii[30]	0	14	44	1 (ref.)
		0.04	48	12	0.08 (0.03–0.19)
Overall estimate (heterogeneity P=0.62, I^2=0%)					0.11 (0.06–0.18)
Sensitivity analysis					0.11 (0.06–0.19)
Tropisetron	Ang[3]	0	8	15	1 (ref.)
		0.1	17	7	0.22 (0.06–0.75)
	Jensen[42]	0	4	32	1 (ref.)
		0.2	19	16	0.11 (0.03–0.36)
Overall estimate (heterogeneity P=0.41, I^2=0%)					0.15 (0.06–0.35)
Dolasetron	Sukhani[94]	0	46	54	1 (ref.)
		0.5	38	11	0.25 (0.10–0.59)
Midazolam	Splinter[80]	0	46	61	0.54
		0.075	63	45	(0.31–0.93)
Gastric aspiration	Jones[43]	0	9	26	1 (ref.)
		Aspiration	6	33	1.9 (0.6–6.0)
Acupuncture	Yentis[107]	No	14	8	1
		Yes	14	9	1.13 (0.34–3.76)
	Shenkman[75]	No	22	31	1
		Yes	19	28	1.05 (0.47–2.32)
	Rusy[71]	No	9	31	1
		Yes	15	25	0.48 (0.18–1.29)
Overall estimate (heterogeneity P=0.42, I^2=0%)					0.83 (0.48–1.43)

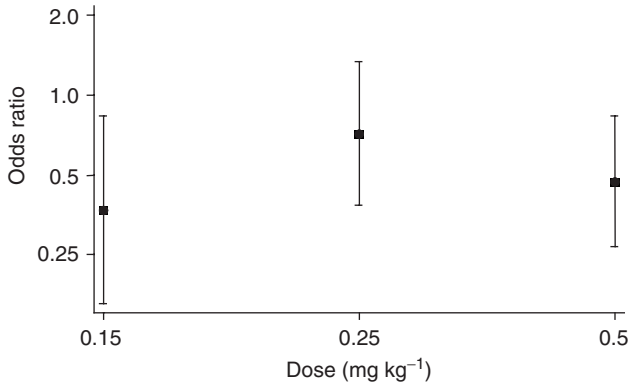

Fig 1 The effect of the dose of metoclopramide on the prevention of POV.

which also included retching in the definition. Drug doses ranged from 0.15 to 0.5 mg kg^{-1} given in single or divided doses. Only one[87] had a standardized anaesthetic technique. All studies dealt with children undergoing tonsillectomy with or without adenoidectomy and follow-up was for 24 h, except for that by Stene and colleagues[87] whose follow-up was for only 4 h. Only two studies established that there was no difference in the use of postoperative opioids.[33 69] Stene and colleagues[87] terminated their trial early based on the results of a favourable interim analysis. One study reported a loss-to-follow-up/protocol violation rate of more than 20%.[33] The summary OR for metoclopramide was 0.51 (95% CI 0.34–0.77). A sensitivity analysis excluding these two studies[87 33] estimated that the OR was 0.39 (95% CI 0.22–0.68). There was no evidence of heterogeneity between studies (I^2=0%). There was no evidence that the effect of metoclopramide varied according to dose (Fig. 1).

Dimenhydrinate

There was one placebo-controlled trial testing dimenhydrinate.[37] It had two interventional arms: dimenhydrinate 0.5 mg kg^{-1} i.v. and ondansetron 0.1 mg kg^{-1} i.v. The trial was terminated early as a result of the occurrence of two significant concealed haemorrhages in the ondansetron group. An analysis was therefore performed after 74 children had been recruited. There was insufficient evidence to suggest that dimenhydrinate was more effective than placebo for the prophylactic control of POV (OR=0.84, 95% CI 0.20–3.65). Whilst the early termination of the trial for safety reasons significantly reduced the power of the study to detect a difference between the dimenhydrinate and placebo groups, it did not invalidate the analysis.

Droperidol

There was only one trial testing droperidol.[33] There was no evidence that droperidol was more effective than placebo (OR=0.99, 95% CI 0.44–2.22). As 20% of participants were lost to follow-up, and no data were presented as to how this loss was distributed between groups, the results of this study are difficult to interpret.

Perphenazine

There was one trial assessing the efficacy of perphenazine.[84] Perphenazine was better at controlling POV than placebo (OR=0.50, 95% CI 0.31–0.82). Subgroup analysis did not suggest that this effect varied according to whether subjects received premedication or what type of induction was used.

Serotonin (5-HT_3) antagonists

Four serotinergic antagonists (ondansetron, granisetron, tropisetron and dolasetron) have been investigated for the control of POV in children after tonsillectomy.

Ondansetron

Ten trials met the inclusion criteria. The definition of POV differed between studies: some authors required the expulsion of gastric contents,[33 68 69] while others also included retching.[7 37 53 87 94] Two did not include a definition.[50 79] Two studies only collected outcome data on the day of surgery.[50 87] The dose of ondansetron used varied between 0.1 and 0.3 mg kg^{-1} given in single or divided doses. One study investigated two different doses of i.v. ondansetron.[69] Most studies investigated the effect of i.v. administration; however, two studies used oral preparations.[68 79] Postoperative opioid administration appeared to be similar between groups in seven studies, but this was not commented on in the other three.[7 87 94] All but one study[37] included children having tonsillectomy with or without adenoidectomy.

The summary OR for the effect of ondansetron combined across all doses was 0.36 (95% CI 0.26–0.46). There was clear evidence of between-study heterogeneity (I^2=57.2%, P=0.013). In a sensitivity analysis excluding three studies including Furst and colleagues[33] (excluded because 20% of participants were lost to follow-up), Litman and colleagues[50] (excluded because there were only 4 h of follow-up together with potential confounding because of unequal use of dexamethasone between study groups), and Stene and colleagues[87] (excluded because of an early termination of trial on the basis of the favourable result of an interim analysis), the summary OR was 0.41 (95% CI 0.32–0.53).

When evidence from all the trials was combined, there was clear evidence that the effect of ondansetron varied according to dose (Fig. 2). Therefore, we used logistic regression to estimate the OR per unit increase in dose in each study (Fig. 3). The summary OR per 0.1 mg kg^{-1} increase in dose, using inverse-variance weighted fixed-effect meta-analysis, was 0.43 (95% CI 0.36–0.51). There was no evidence of heterogeneity in the dose–response effect of ondansetron (I^2=10.4%, P=0.35), and no evidence that the effect of the i.v. preparation was more effective than the oral preparation. However, an asymmetrical funnel plot (Fig. 4) suggests that small studies tended to find larger dose–response effects of ondansetron (Egger's test, P<0.001).

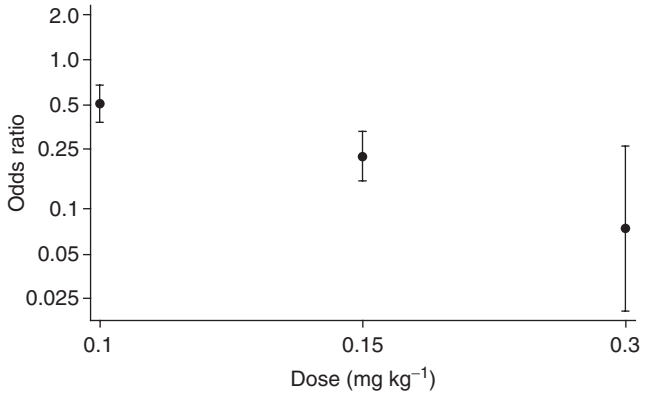

Fig 2 The effect of the dose of ondansetron on the incidence of POV.

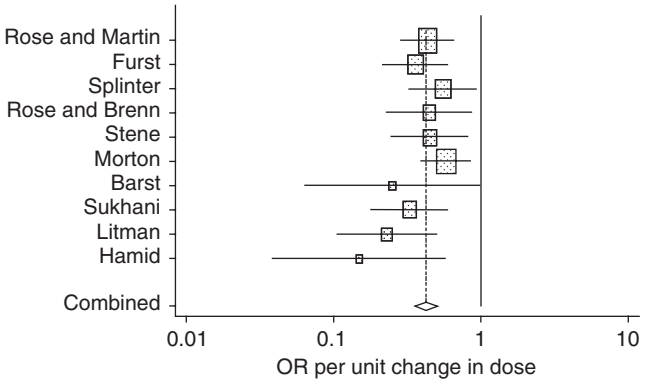

Fig 3 Forest plot showing the dose–response effect of ondansetron (OR per unit change in dose, estimated using logistic regression) together with the summary OR estimated using fixed-effect inverse-variance weighted meta-analysis.

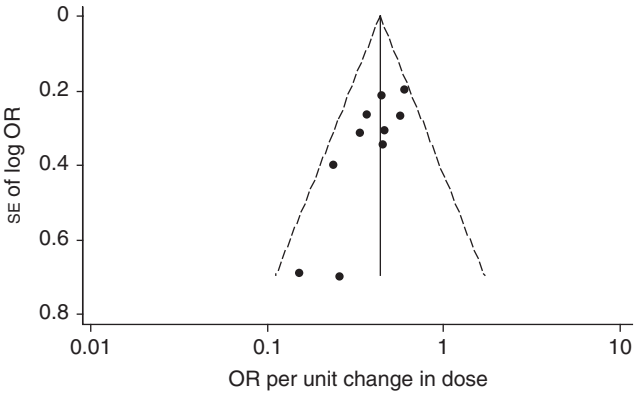

Fig 4 A funnel plot of all studies investigating ondansetron showing evidence of 'small-study' bias.

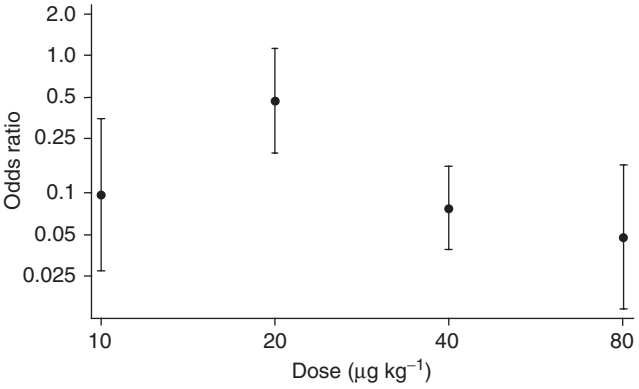

Fig 5 The effect of the dose of granisetron on the prevention of POV.

Granisetron

There were three relevant trials.[9 25 30] Vomiting was not defined in one[9] and was considered to include retching in the other two. The follow-up period was for 24 h for all studies; however, the way the data are presented in one[9] meant that only data during the day of surgery could be included in the analysis. One study used oral granisetron[25] and doses ranged from 10 to 80 μg kg^{-1} (oral or i.v.). In two studies there were no differences between groups in the use of opioids, but this was not considered in the other.[9]

There was clear evidence that administration of granisetron reduced the incidence of POV (OR=0.11, 95% CI 0.06–0.18). There was no evidence of between-study heterogeneity (I^2=0%).

In a sensitivity analysis excluding the study by Carnahan and colleagues,[9] because of the issues outlined above, the estimated effect was unchanged (OR=0.11, 95% CI 0.06–0.19). There was no evidence of a dose–response effect for granisetron (Fig. 5).

Tropisetron

Two trials met the inclusion criteria.[3 42] Both used the same definition of vomiting, follow-up period and route of administration. The doses used were 0.1 and 0.2 mg kg^{-1}, and the administration of postoperative opioids did not differ between intervention and control groups, but one[42] did not use a standardized anaesthetic technique. The authors investigated the possibility of confounding as a result of this, but were unable to find any significant differences between the groups.

The summary OR for the effect of tropisetron on POV was 0.15 (95% CI 0.06–0.35). There was no evidence of heterogeneity between groups (I^2=0%). Figure 6 shows that the effect of tropisetron appears to increase with dose.

Dolasetron

Only one published trial has tested the efficacy of dolasetron.[94] This was a small study using a standardized anaesthetic technique. Dolasetron had a clinically important treatment effect (OR=0.25, 95% CI 0.1–0.59). The use of postoperative opioids was not reported.

Pooled estimate for anti-serotinergic agents

We performed a pooled estimate of the overall effect of anti-serotinergic agents using the data from the most effective dose of each of the four drugs. The summary OR for anti-serotinergic agents combined was 0.12 (95% CI 0.07–0.20) using a fixed effect model. Although

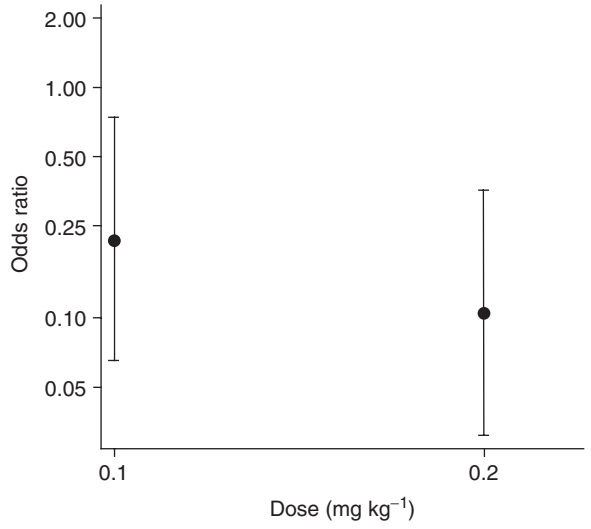

Fig 6 The effect of the dose of tropisetron on the prevention of POV.

inter-study heterogeneity accounted for much of the variation seen (I^2=45.6%), overall it did not reach a significant level (P=0.14).

Midazolam

We identified one trial that investigated the effect of midazolam.[80] No definition of vomiting was given. Neither the completeness of follow-up nor the differential use of postoperative opioids was commented on. The results indicated a modest reduction in the incidence of POV associated with the use of i.v. midazolam (OR=0.54; 95% CI 0.31–0.93).

Dexamethasone

Steward and colleagues[91] published a meta-analysis of seven double-blind, randomized placebo-controlled trials of dexamethasone in 2001. Doses ranged from 0.15[82] to 1 mg kg^{-1}.[5 60 97] The summary RR calculated was 0.55 (95% CI 0.41–0.74). Two further trials[4 19] have been published as that would have met their inclusion criteria, and hence the meta-analysis for POV was re-performed. The dose used in both studies was 0.5 mg kg^{-1} (maximum dose of 8 mg). The summary RR incorporating these studies was 0.48 (95% CI 0.40–0.57) while the summary OR was 0.23 (95% CI 0.16–0.33). There was no strong evidence of significant inter-study heterogeneity (P=0.24).

Non-pharmacological strategies

Gastric evacuation

Blood is known to be extremely irritant to the stomach and likely to induce vomiting. The evacuation of gastric contents under anaesthesia has been advocated as a means of reducing POV after ENT surgery.[61] Only one trial investigating this phenomenon met the inclusion criteria.[43] The anaesthetic and surgical techniques were standardized, and no prophylactic anti-emetic agents were used. No reference is made to the differential use of postoperative opioids between groups. Gastric evacuation was associated with an increase in the incidence of POV (OR=1.9, 95% CI 0.6–6.0), although the sample size limited the precision of the estimate. Neither the frequency of vomiting nor the need for rescue anti-emetics differed between the two groups.

Acupuncture

Three trials were identified.[71 75 107] One[107] included only tonsillectomy patients whilst the other two studies included patients who may also have had adenoidectomy. One[71] defined a vomit as producing gastric contents, whilst the other two also included retching. All studies used the P6 acupuncture site on the ventral surface of the lower forearm although there was variation in the mode of stimulation (Table 1). All studies used standardized anaesthetic techniques and there was no difference identified in the administration of postoperative opioids between groups.

The summary OR for acupuncture was 0.83 (95% CI 0.45–1.4). There was no evidence of heterogeneity between studies (I^2=0%).

Discussion

The results of this systematic review indicate that there is good evidence that the anti-serotinergic agents ondansetron, granisetron and tropisetron are clinically effective, and that there is a dose–response effect. The evidence for dolasetron, although weaker, also suggests that it is a suitable agent for the prophylactic control of POV in this patient group. The results of the pooled anti-serotinergic analysis are consistent with the literature in other patient groups which indicate that this group of drugs are highly effective anti-emetic agents.[47 63 72 74 105]

Meta-analysis of the studies investigating the effect of metoclopramide suggests that it is also an effective agent. The limited data on higher doses of metoclopramide does not support the hypothesis that higher doses have increased clinical efficacy. This conclusion should be interpreted with caution because of the small amount of available data. There are not enough data available to allow a conclusion to be made about the effects of both perphenazine and midazolam, nor the absence of effect for dimenhydrinate, droperidol, gastric aspiration and acupuncture. The inclusion of two further relevant studies into the published meta-analysis of dexamethasone[91 92] gave results consistent with the original findings. This provides good evidence of the efficacy of dexamethasone for the prophylactic control of POV.

The use of POV as an outcome remains contentious. It has been proposed that it represents a surrogate endpoint that does not necessarily reflect what have been termed the 'true' endpoints of delayed recovery discharge, unplanned overnight admission and reduced patient satisfaction.[21]

The alternative viewpoint, however, defends its use by recognizing that many patients consider POV more undesirable than postoperative pain.[101] POV is easily measured and almost universally used by researchers. This, together with the effect that POV has on patient and parent satisfaction supports its use as a primary outcome.[16 34]

The incidence of POV in children undergoing tonsillectomy with or without adenoidectomy is sufficiently high (up to 70%[20 33 37 42]) to warrant the use of effective anti-emetic prophylaxis rather than relying solely on rescue therapy.[35] The complexity of POV makes the identification and avoidance of relevant triggers, be they patient, surgical or anaesthetic, extremely difficult. This provides a strong argument for prophylaxis and hence the need for a systematic review of the literature.

By design, only double-blind, randomized, placebo-controlled trials were included in this meta-analysis. Whilst the measurement of POV is unlikely to be significantly affected by reporter bias associated with a lack of blinding, no single-blind/unblinded, randomized, placebo-controlled trials were identified. The choice of a fixed effect model was justified in each analysis by calculating the heterogeneity between studies (I^2) and by a comparison with random effects model. Evidence of heterogeneity was found amongst the studies of ondansetron; however, much of this variation was subsequently found to be because of dose-variation. Variations between studies in terms of the definition of vomiting used, the route of administration and dose of drug used, the anaesthetic technique used, the surgery, the length and completeness of the follow-up, and postoperative analgesia were documented, and together with an assessment of the methodology, guided the exclusion of studies in the sensitivity analyses.

A decision was made to exclude the surgical details from the analysis. It is possible that the surgical technique could influence the incidence of POV, although there is no evidence to support or refute this hypothesis. The variable reporting of surgical details in the POV literature, which is almost entirely published by anaesthetists, further clouds the issue. It was assumed that the confounding influence of any of these variables was minimized by the process of randomization used in each study.

An assessment of the likelihood of publication bias was made by plotting funnel plots and using the regression test proposed by Egger and colleagues.[18] Studies showing a significant treatment effect are more likely to be published than those with negative results.[89] Smaller studies require a larger treatment effect to reach statistical significance. They are consequently less likely to produce a positive result and hence more likely to be rejected by journals. The inclusion of published smaller studies in a systematic review is likely, therefore, to overestimate any real treatment effect. Larger studies on the other hand are more likely to be published even without a positive result by virtue of their size. The funnel plot for ondansetron was asymmetrical. This provides evidence of 'small study effects' and suggests that the summary OR may have been overestimated. Funnel plot analysis was not used for any of the other drugs because of the limited number of studies available for analysis.

This systematic review focuses on single therapy for prophylaxis in an attempt to identify the efficacy of individual agents. The use of a single anti-emetic for prophylaxis in this patient group is however uncommon with many clinicians using steroids as adjuvant therapy. Despite this, little has been published about combined therapies.[41]

Conclusions

This systematic review and meta-analysis provides good evidence that dexamethasone and the serotinergic antagonists ondansetron, granisetron and tropisetron are clinically effective agents for the prophylactic control of POV in children after tonsillectomy with or without adenoidectomy. There is also evidence to suggest that metoclopramide is also an effective agent. Whilst there is some evidence that perphenazine and midazolam may be effective agents, this evidence has not been corroborated. There is currently insufficient evidence to suggest that dimenhydrinate, droperidol, gastric aspiration or acupuncture are clinically useful in this setting.

Acknowledgements

This study was funded by Research Scholarship Grants for the principal author from National Health and Medical Research Council of Australia and The Australian and New Zealand College of Anaesthetists.

Appendix

Table A1 Studies excluded from the review. 1, not limited to children; 2, not double-blind, randomized and placebo-controlled; 3, insufficient data given; 4, not solely tonsillectomy or adenotonsillectomy; 5, not published in or translated into English; 6, either not an anti-emetic drug used or not administered prophylactically; 7, included in Steward's sytematic review of dexamethasone in children undergoing tonsillectomy[91]

Study (primary author)	Reason for exclusion
Anderson[2]	2,6
Anderson[1]	2,6
Barst[6]	2
Carithers[8]	2
Chhibber[11]	2,6
Church[12]	2
Cohn[13]	2
Courtman[14]	2
Culy[15]	2
Dillier[17]	5
Fujii[23]	4

Table A1 *Continued*

Study (primary author)	Reason for exclusion
Fujii[28]	2
Fujii[29]	2
Fujii[31]	2
Fujii[32]	2
Fujii[22]	4
Fujii[24]	4
Fujii[26]	2
Guida[36]	2
Heatley[38]	2
Hellier[39]	2
Hengerer[40]	2
Holt[41]	2
Kanerva[44]	2
Kearney[45]	6
Kermode[46]	2
Lawhorn[49]	4
Lawhorn[48]	3
Madadaki[51]	5
Moiniche[52]	2
Mukherjee[54]	2,6
Nolan[55]	2
O'Flaherty[56]	6
Panarese[58]	2
Pandit[59]	6
Pappas[60]	7
Patel[62]	2
Roberts[64]	2
Romsing[65]	6
Rose[66]	2
Rose[67]	2
Shott[76]	2
Splinter[86]	4
Semple[73]	2.6
Smith[77]	2
Splinter[85]	2
Splinter[83]	2
Splinter[78]	2
Splinter[81]	2
Steward[90]	2
Steward[92]	2
Steward[91]	2
Stewart[93]	2
Sutherland[95]	2,6
Thomas[96]	2
Walker[104]	2
van den Berg[100]	1
van den Berg[99]	1
van den Berg[98]	4
Ved[102]	6
Watters[106]	6
Zatman[108]	2
Zestos[109]	6

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