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How Much Does Pharmacologic Prophylaxis Reduce Postoperative Vomiting in Children?

Calculation of Prophylaxis Effectiveness and Expected Incidence of Vomiting under Treatment Using Bayesian Meta-analysis

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Background: **The authors calculated the effect size for treatments recommended for the pediatric population in the new Guidelines for the Management of Postoperative Nausea and Vomiting that should be implemented with the help of a new risk scale developed for children.**

Methods: **Six single-drug therapies and five combination treatments were subjected to a Bayesian analysis, with respect to the outcome reported, in a sequence that parallels their dates of publication. Based on the Bayes theorem, a posterior probability was calculated after inclusion of the data from the successive studies, to update a prior probability existing before inclusion of that study. The posterior for the preceding group of trials served as the prior for the subsequent trial. The final odds ratio with its 95% credibility interval compared with placebo is considered as the results for that treatment, and was transformed into a relative risk whose 95% credibility interval allows the calculation of a most pessimistic and a most optimistic incidence of postoperative vomiting.**

Results: **The most pessimistic expectations with the 5-hydroxytryptamine receptor antagonists and dexamethasone result in a 50–60% relative risk reduction. The results with droperidol offer a decrease of only approximately 40%. With the combinations of a 5-hydroxytryptamine receptor antagonist and dexamethasone, a relative risk reduction of approximately 80% is expected.**

Conclusions: **The authors' tables list the expected incidence of postoperative vomiting with each treatment for each risk category, and the expected relative risks that can be used with baseline risk values from any source.**

RECENTLY, a new set of Guidelines for the Management of Postoperative Nausea and Vomiting has been published.[1] These guidelines contain extensive recommendations for treatment in children and should be implemented with the help of a new risk scale developed for children.[2] Despite the description of several pharmacologic therapies using single drugs or combinations, no precise expected size of treatment effect is given in these guidelines.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

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The aim of this article is to calculate the various effect sizes for each treatment recommended in the pediatric population, expressed as a relative risk (RR) that can be obtained using the treatments suggested in the new guidelines. Once these RRs are obtained, the risk of postoperative vomiting can be computed for each of the risk categories described in the new pediatric risk scale.

Materials and Methods

This article considers the efficacy of six single-drug therapies and five combination treatments. The single drugs are ondansetron, tropisetron, granisetron, dolasetron, dexamethasone, and droperidol. The combinations for which there is an existing pediatric literature are ondansetron plus dexamethasone, ondansetron plus droperidol, tropisetron plus dexamethasone, dolasetron plus dexamethasone, and granisetron plus dexamethasone. All of these treatments were administered by the intravenous route during surgery, with the exception of two ondansetron, one ondansetron plus dexamethasone, one granisetron, and one dolasetron trial, where they were given orally before surgery.

Search Strategy

We looked for controlled trials, including only children, in the postoperative setting, and in which the incidence of postoperative vomiting or nausea was one of the endpoints. The comparator had to be a placebo for the single-drug treatments; for the combination treatments, one of the drugs in the combination, or placebo, had to serve as the comparator. We included only treatments listed in the new Guidelines for the Management of Postoperative Nausea and Vomiting.[1]

For ondansetron, we searched PubMed with the search criteria *ondansetron* and *postoperative*, with the limits human clinical trials and children aged 0–18 yr. This search produced a list of 174 articles. These articles were searched manually and produced 14 trials[3–16] comparing ondansetron with a placebo. Five trials compared ondansetron plus dexamethasone with ondansetron[14,17] or dexamethasone[18–20] alone, and in one study,[14] a placebo was also used as a comparator. The remainder comprised 59 trials in adults, 43 trials that were not adequately controlled, 47 trials in which postoperative

vomiting or nausea was not an endpoint or that were not in the postoperative setting, or did not concern ondansetron at all. Seven articles were reviews or meta-analyses.

For tropisetron, we searched PubMed with the search criterion *tropisetron*, with human clinical trials and children aged 0–18 yr used as limits. The search produced

Table 1. List of All Included Trials

Study	Endpoint	Emetic Symptom Explicitly Excluded from Analysis	Duration of Assessment	Exclusion of Children with Previous PONV, Motion Sickness, or Emesis during the 24 Preoperative Hours
Ondansetron				
Furst[3]	Vomiting	No	First 24 h	No
Litman[4]	Vomiting	No	First 24 h	No*†
Splinter[5]	Vomiting	No	First 24 h	No
Rose[6]	Vomiting	Retching or gagging	First 24 h	Yes§‖#
Stene[7]	Vomiting or retching	No	First 24 h	No
Morton[8]	Vomiting or retching	No	First 24 h	No*
Patel[11]	Vomiting or retching	No	First 24 h	Yes‡§
Hamid[9]	Vomiting or retching	No	First 24 h	Yes‡§
Barst[10]	Vomiting or retching	Nausea	First 24 h	Yes#
Subramaniam[12]	Nausea or vomiting	No	First 24 h	No§
Shende[13]	Nausea or vomiting	No	First 24 h	No*†
Karamanlioglu[16]	Nausea or retching or vomiting	No	First 24 h	No§
Bhardwaj[14]	Vomiting	No	First 24 h	No
Khalil[15]	Vomiting or retching	No	First 24 h	Yes‡§
Tropisetron				
Ang[21]	Vomiting or retching	No	First 24 h	No
Allen[22]	Vomiting or retching	Vomiting at tracheal extubation	First 24 h	No§
Jenssen[23]	Vomiting or retching	No	First 24 h	No
Dillier[24]	Vomiting	No	First 24 h	Yes‡§
Tosun[25]	Vomiting or retching	No	First 24 h	No§
Dolasetron				
Wagner[28]	Vomiting or retching	No	First 24 h	Yes§‖#
Karamanlioglu[16]	Nausea or retching or vomiting	No	First 24 h	No§
Granisetron				
Cieslak[36]	Vomiting or retching	Nausea	First 24 h	No§
Munro[37]	Vomiting or retching	No	First 24 h	No§
Gombar[38]	Vomiting or retching	Nausea	First 24 h	Yes§‖#††
Dexamethasone				
Catlin[40]	Required antiemetic therapy	No	Not reported	No
Splinter[41]	Vomiting	Retching and nausea	First 24 h	No
Mathew[42]	Nausea or vomiting	No	First 24 h	Yes§‖#
Ohlms[57]	Vomiting	No	First 24 h	No
Tom[44]	Vomiting	No	First 24 h	No
April[45]	Vomiting	No	First 6 h	No
Pappas[46]	Vomiting or retching	Nausea	First 24 h	No§
Vosdoganis[47]	Vomiting	No	First 24 h	Yes‖
Aouad[48]	Vomiting	Nausea	First 24 h	No§
Subramaniam[12]	Nausea or vomiting	No	First 24 h	No§
Elhakim[50]	Vomiting	Nausea	First 24 h	No§
Madan[43]	PONV	No	First 24 h	Yes§‖#
Riad[51]	Vomiting	No	First 24 h	No
Droperidol				
Rita[52]	Vomiting or retching	No	First 24 h	No**
Lunn[53]	Vomiting or retching	No	At least 24 h	No*†
Shende[13]	Nausea or vomiting	No	First 24 h	No*†
Ondansetron plus dexamethasone				
Rose[18]	Vomiting	Retching or gagging	First 24 h	Yes§‖#
Splinter[17]	Vomiting	Retching	First 48 h	No
Splinter[19]	Vomiting	Retching	First 48 h	No
Sukhani[20]	Vomiting or retching	Nausea	First 24 h	No§
Bhardwaj[14]	Vomiting	No	First 24 h	No
Tropisetron plus dexamethasone				
Holt[26]	Vomiting	Retching	First 24 h	Yes†‖
Liechti[27]	Vomiting or retching	No	First 24 h	No§
Dolasetron plus dexamethasone				
Sukhani[20]	Vomiting or retching	Nausea	First 24 h	No§
Granisetron plus dexamethasone				
Gombar[38]	Vomiting or retching	Nausea	First 24 h	Yes§‖#††
Ondansetron plus droperidol				
Shende[13]	Nausea or vomiting	No	First 24 h	No*†

* Children with history of postoperative nausea and vomiting (PONV) explicitly included. † Children with history of motion sickness explicitly included. ‡ Children with history of vomiting during the past 24 h explicitly excluded. § Children receiving medication with antiemetic properties before the start of the study explicitly excluded. ‖ Children with history of PONV explicitly excluded. # Children with history of motion sickness explicitly excluded. ** Children who received morphine or meperidine postoperatively for pain eliminated from the study. †† Children with gastroesophageal reflux explicitly excluded.

Table 2. Ondansetron *vs.* Placebo: List of Trials

Study	Year	Surgery	Dose, mg/kg	Age Min, yr	Age Max, yr
Furst[3]	1994	Tonsillectomy	0.15	2	12
Litman[4]	1994	Tonsillectomy	0.15	3	
Splinter[5]	1995	Tonsillectomy	0.1 oral	2	14
Rose[6]	1996	Tonsillectomy	0.15–0.3	2	12
Stene[7]	1996	Tonsillectomy	0.15	2	12
Morton[8]	1997	Tonsillectomy	0.1	1	12
Patel[11]	1997	Tonsillectomy Strabismus Herniorrhaphy Orchidopexy	0.1	1	12
Hamid[9]	1998	Tonsillectomy	0.1	2	10
Barst[10]	1999	Tonsillectomy	0.1	1	18
Subramaniam[12]	2001	Strabismus	0.1	2	15
Shende[13]	2001	Strabismus	0.15	1	15
Karamanlioglu[16]	2003	Strabismus Middle ear surgery Adenotonsillectomy Orchidopexy	0.15 oral	*	
Bhardwaj[14]	2004	Strabismus	0.15	2	12
Khalil[15]	2005	Adenoidectomy Myringotomy Orchidopexy Plastic surgery Hernia repair Orthopedic	0.1	1 month	2

* No range given. Mean ± SD: 9.7 ± 3.2 yr.

45 trials. Five trials[21–25] using tropisetron alone and 1 trial[26] using tropisetron plus dexamethasone were found in this list. Twenty-five trials were in the setting of chemotherapy, 2 trials were not placebo controlled, 7 trials were in fact in adults, and in 5 trials postoperative nausea or vomiting was not an endpoint or they were not in the postoperative setting. Using the key words *postoperative* and *tropisetron* produced 1 trial[27] using tropisetron plus dexamethasone that was not in the previous list.

For dolasetron, we searched PubMed with the search criterion *dolasetron*, with human clinical trials and children aged 0–18 yr used as limits. The search produced 22 trials. Two trials[16,28] using dolasetron alone and a single trial[20] using dolasetron plus dexamethasone were found in this list. Two trials were in the setting of chemotherapy, 2 trials were not placebo controlled, 8 trials were in fact in adults, and in 7 trials postoperative nausea or vomiting was not an endpoint or they were not in the postoperative setting. Using the key words

Table 3. Ondansetron *vs.* Placebo: Results

	Ondansetron		Placebo		Ondansetron		Placebo		Log OR before Inclusion of This Trial	SD before Inclusion of This Trial	Log OR after Inclusion of This Trial	SD after Inclusion of This Trial	Odds Ratio [95% Credibility Interval] after Inclusion of This Trial
Study	n	POV	n	POV	n Total	POV Total	n Total	POV Total					
Furst[3]	61	16	61	38	61	16	61	38	0	10	−1.506	0.388	0.22 [0.10–0.47]
Litman[4]	30	7	30	22	91	23	91	60	−1.506	0.388	−1.633	0.249	0.20 [0.12–0.32]
Splinter[5]	109	43	124	67	200	66	215	127	−1.633	0.249	−1.296	0.158	0.27 [0.20–0.37]
Rose[6]	40	9	40	20	240	75	255	147	−1.296	0.158	−1.211	0.121	0.30 [0.26–0.38]
Stene[7]	43	11	47	25	283	86	302	172	−1.211	0.121	−1.176	0.099	0.31 [0.25–0.37]
Morton[8]	212	85	215	115	495	171	517	287	−1.176	0.099	−1.059	0.079	0.35 [0.30–0.40]
Patel[11]	210	67	215	129	705	238	732	416	−1.059	0.079	−1.021	0.064	0.36 [0.32–0.41]
Hamid[9]	25	10	44	36	730	248	776	452	−1.021	0.064	−1.014	0.055	0.36 [0.33–0.40]
Barst[10]	45	3	45	10	775	251	821	462	−1.014	0.055	−1.008	0.049	0.36 [0.33–0.40]
Subramaniam[12]	45	6	45	19	820	257	866	481	−1.008	0.049	−1.008	0.044	0.36 [0.33–0.40]
Shende[13]	60	22	60	38	880	279	926	519	−1.008	0.044	−1.008	0.04	0.36 [0.34–0.39]
Karamanlioglu[16]	50	24	50	39	930	303	976	558	−1.008	0.04	−1.009	0.037	0.36 [0.34–0.39]
Bhardwaj[14]	39	13	39	20	969	316	1,015	578	−1.009	0.037	−1.008	0.034	0.36 [0.34–0.39]
Khalil[15]	335	38	335	93	1,304	354	1,350	671	−1.008	0.034	−1.003	0.031	0.37 [0.35–0.39]

Log OR = natural logarithm of the odds ratio; n = number of children in the group; POV = number of children presenting the postoperative endpoint; SD = SD of the distribution of the natural logarithm of odds ratios.

Table 4. Tropisetron *vs.* Placebo

Study	Year	Surgery	Dose, mg/kg	Age Min, yr	Age Max, yr	Tropisetron n	Tropisetron POV	Placebo n	Placebo POV	Odds Ratio [95% Credibility Interval] after Inclusion of This Trial
Ang[21]	1998	Tonsillectomy	0.1	2	12	24	7	23	15	0.24 [0.07–0.78]
Allen[22]	1999	Appendicectomy Orthopedic Other	0.1	7	15	29	6	27	19	0.18 [0.09–0.36]
Jenssen[23]	2000	Tonsillectomy	0.2	2	14	35	16	36	32	0.17 [0.10–0.27]
Dillier[24]	2000	Tonsillectomy	0.1	2	12	49	17	49	32	0.18 [0.13–0.25]
Tosun[25]	2006	Strabismus	0.5–2 mg/m^2	2	12	100	19	25	15	0.17 [0.13–0.22]

n = number of children in the group; POV = number of children presenting the postoperative endpoint.

postoperative and *dolasetron* did not allow us to find other trials.

For granisetron, we searched PubMed with the search criterion *granisetron*, with human clinical trials and children aged 0–18 yr used as limits. The search produced 79 trials. However, it must be noted that serious doubts[29] have been expressed about the validity of the studies from Fujii *et al.*; they were therefore excluded from our analysis, and the list was reduced to 57 after exclusion of the trials by Fujii *et al.*, including 4 trials[30–33] in children using granisetron alone and 2 trials[34,35] with a combination of granisetron plus dexamethasone. Three trials[36–38] using granisetron alone and 1 trial[38] using granisetron plus dexamethasone were found in this list and are included in our analysis. Forty-one trials were in the setting of chemotherapy, 3 trials were not placebo controlled, 3 trials were in fact in adults, and in 7 trials postoperative nausea or vomiting was not an endpoint or they were not in the postoperative setting. Using the key words *postoperative* and *granisetron* did not allow us to find other trials.

For dexamethasone, we searched PubMed for the simultaneous key words *dexamethasone*, *children*, and *postoperative*. This produced a list of 68 articles. One trial was in adults, 3 trials were not placebo controlled, in 49 articles postoperative vomiting was not an endpoint or they were general review articles or were not in the postoperative setting, and 1 article was a meta-analysis.[39] Three trials concerned combination treatments (ondansetron plus dexamethasone). Twelve randomized controlled trials[40–51] were included in our analysis. Searching for key words *tonsillectomy* and *dexametha-*

Table 5. Dolasetron *vs.* Placebo

Study	Year	Surgery	Dose, mg/kg	Age Min, yr	Age Max, yr	Dolasetron n	Dolasetron POV	Placebo n	Placebo POV	Odds Ratio [95% Credibility Interval] after Inclusion of This Trial
Wagner[28]	2003	Strabismus	0.35 or 12.5-mg fix	2	12	76	14	18	9	0.23 [0.08–0.68]
Karamanlioglu[16]	2003	Strabismus Middle ear surgery Adenotonsillectomy Orchidopexy	1.8 oral	*		50	16	50	39	0.16 [0.09–0.27]

* No range given. Mean ± SD: 10.0 ± 2.8 yr.

n = number of children in the group; POV = number of children presenting the postoperative endpoint.

Table 6. Granisetron *vs.* Placebo

Study	Year	Surgery	Dose, mg/kg	Age Min, yr	Age Max, yr	Granisetron n	Granisetron POV	Placebo n	Placebo POV	Odds Ratio [95% Credibility Interval] after Inclusion of This Trial
Cieslak[36]	1996	Strabismus Tonsillectomy Dental	0.04	2	16	33	3	31	13	0.18 [0.08–0.43]
Munro[37]	1999	Strabismus	0.04 oral	1	12	24	7	25	21	0.15 [0.07–0.30]
Gombar[38]	2007	Middle ear surgery	0.04	3	12	30	6	30	15	0.16 [0.20–0.45]

n = number of children in the group; POV = number of children presenting the postoperative endpoint.

Table 7. Dexamethasone *vs.* Placebo

Study	Year	Surgery	Dose, mg/kg	Age Min, yr	Age Max, yr	Dexamethasone		Placebo		Odds Ratio [95% Credibility Interval] after Inclusion of This Trial
						n	POV	n	POV	
Catlin[40]	1991	Tonsillectomy	0.15	4	12	10	3	15	7	0.53 [0.11–2.63]
Ohlms[57]	1995	Tonsillectomy	0.5	3	18	34	2	35	3	0.54 [0.21–1.34]
Splinter[41]	1996	Tonsillectomy	0.15	2	12	63	25	70	50	0.43 [0.27–0.68]
Tom[44]	1996	Tonsillectomy	1.0	1	18	26	1	32	15	0.37 [0.26–0.53]
April[45]	1996	Tonsillectomy	1.0	3	15	41	2	39	10	0.34 [0.26–0.45]
Pappas[46]	1998	Tonsillectomy	1.0	2	12	63	30	65	57	0.32 [0.27–0.39]
Vosdoganis[47]	1999	Tonsillectomy	0.4	2	12	22	10	19	10	0.32 [0.27–0.39]
Aouad[48]	2001	Tonsillectomy	0.5	2	12	53	12	53	27	0.32 [0.27–0.38]
Subramaniam[12]	2001	Strabismus	1.0	2	15	45	11	45	34	0.31 [0.27–0.36]
Elhakim[50]	2003	Tonsillectomy	0.5	4	11	55	11	55	31	0.30 [0.26–0.34]
Mathew[42]	2004	Strabismus	0.05–0.25	2	15	158	83	42	39	0.31 [0.27–0.35]
Madan[43]	2005	Strabismus	0.25–1.0	2	15	125	30	41	27	0.31 [0.28–0.34]
Riad[51]	2007	Strabismus	0.5	4	12	25	8	25	12	0.31 [0.28–0.34]

n = number of children in the group; POV = number of children presenting the postoperative endpoint.

sone, and *strabismus* and *dexamethasone* did not produce other trials.

For droperidol, we searched PubMed for the key words *droperidol*, *postoperative*, and *children*, with the limits clinical trials and age 0–18 yr. This search produced 66 articles. Only 3 trials[13,52,53] were included in our analysis; it must be noted that only studies using a low dose of 5–25 μg/kg droperidol are included, as higher doses are not recommended in the new guidelines because of the higher rate of extrapyramidal syndrome reported in children. One of these trials also compared ondansetron plus droperidol with a placebo.[13]

Twelve trials used a high dose (≥ 50 μg/kg) of droperidol, 20 trials were not properly controlled by our definition, 2 articles were reviews, and in 29 articles postoperative vomiting was not an endpoint or they were not in the postoperative setting or were completely unrelated to the prevention of postoperative vomiting by droperidol.

We cross-checked the lists of trials that we obtained by this search strategy with the trials included in the Cochrane review,[54] the latest meta-analysis on ondansetron,[55] dexamethasone,[39] and droperidol[56] in children, and we could identify one more trial regarding

Table 8. Droperidol *vs.* Placebo

Study	Year	Surgery	Dose, μg/kg	Age Min, yr	Age Max, yr	Droperidol		Placebo		Odds Ratio [95% Credibility Interval] after Inclusion of This Trial
						n	POV	n	POV	
Rita[52]	1981	Orthopedic	5	1	15	85	23	83	38	0.44 [0.23–0.84]
Lunn[53]	1995	Inguinal hernia Circumcision Hydrocele ligation Orchidopexy Umbilical hernia Miscellaneous	20	1	15	140	34	122	42	0.51 [0.36–0.71]
Shende[13]	2001	Strabismus	25	1	15	60	19	60	38	0.48 [0.37–0.61]

n = Number of children in the group; POV = Number of children presenting the postoperative endpoint.

Table 9. Ondansetron plus Dexamethasone *vs.* Ondansetron or Dexamethasone Alone

Study	Year	Surgery	Ondansetron, mg/kg	Dexamethasone, mg/kg	Age Min, yr	Age Max, yr	Ondansetron + Dexamethasone		Ondansetron or Dexamethasone		Odds Ratio [95% Credibility Interval] after Inclusion of This Trial
							n	POV	n	POV	
Rose[18]	1996	Tonsillectomy	0.15 oral	0.1	1.5	12	46	7	45	17	0.31 [0.12–0.83]
Splinter[17]	1998	Strabismus	0.05	0.15	2	14	99	9	98	27	0.29 [0.17–0.49]
Splinter[19]	2001	Strabismus	0.05	0.15	2	14	111	6	82	19	0.27 [0.18–0.39]
Sukhani[20]	2002	Tonsillectomy	0.15	1	2	12	50	9	50	27	0.26 [0.20–0.35]
Bhardwaj[14]	2004	Strabismus	0.15	0.2	2	12	30	3	39	13	0.25 [0.20–0.31]

n = number of children in the group; POV = number of children presenting the postoperative endpoint.

Table 10. Tropisetron plus Dexamethasone *vs.* Tropisetron Alone

Study	Year	Surgery	Tropisetron, mg/kg	Dexamethasone, mg/kg	Age Min, yr	Age Max, yr	Tropisetron + Dexamethasone n	Tropisetron + Dexamethasone POV	Tropisetron n	Tropisetron POV	Odds Ratio [95% Credibility Interval] after Inclusion of This Trial
Holt[26]	2000	Tonsillectomy	0.1	0.5	2	12	66	17	59	31	0.32 [0.15–0.67]
Liechti[27]	2007	Tonsillectomy	0.1	0.15	1	11	45	11	45	24	0.31 [0.20–0.49]

n = number of children in the group; POV = number of children presenting the postoperative endpoint.

dexamethasone.[57] The 2 additional trials found in the meta-analysis of Henzi *et al.*[56] were not selected because of the use of a high dose (50 and 75 μg/kg) of droperidol.

All of the trials were prospective randomized controlled trials, with one exception,[27] which was a retrospective study with matching controls.

For all drugs, different doses of the same drug were used by different authors. For ondansetron (0.1–0.3 mg/kg), tropisetron (0.1–0.2 mg/kg), and droperidol (5–25 μg/kg), the difference between the highest and lowest dose was not excessively different. For all of these drugs, the obvious decision was to make a single analysis with all doses grouped together. With granisetron, the guidelines[1] recommend only 40 μg/kg, which was the dose selected for our analysis. But for dexamethasone, the doses ranged from 0.050 to 1.0 mg/kg, a 20-fold difference. However, 3 trials included a dose-ranging study; ranges from 0.050 to 0.250 mg/kg,[42] 0.250 to 1.0 mg/kg,[43] and 0.0625 to 1.0 mg/kg[58] were studied, and there was no indication of a dose response. Therefore, we decided to make a single analysis with all doses grouped together.

Table 11. Dolasetron plus Dexamethasone *vs.* Dolasetron Alone

Study	Year	Surgery	Dolasetron, mg/kg	Dexamethasone, mg/kg	Age Min, yr	Age Max, yr	Dolasetron + Dexamethasone n	Dolasetron + Dexamethasone POV	Dolasetron n	Dolasetron POV	Odds Ratio [95% Credibility Interval] after Inclusion of This Trial
Sukhani[20]	2002	Tonsillectomy	0.5	1.0	1	12	49	13	50	28	0.29 [0.13–0.67]

n = number of children in the group; POV = number of children presenting the postoperative endpoint.

Table 12. Granisetron plus Dexamethasone *vs.* Placebo

Study	Year	Surgery	Granisetron, mg/kg	Dexamethasone, mg/kg	Age Min, yr	Age Max, yr	Granisetron + Dexamethasone n	Granisetron + Dexamethasone POV	Placebo n	Placebo POV	Odds Ratio [95% Credibility Interval] after Inclusion of This Trial
Gombar[38]	2007	Middle ear surgery	0.04	0.150	3	12	30	1	30	15	0.05 [0.001–0.31]

n = number of children in the group; POV = number of children presenting the postoperative endpoint.

Table 13. Ondansetron plus Droperidol *vs.* Placebo and Ondansetron plus Dexamethasone *vs.* Placebo

Study	Year	Surgery	Ondansetron, mg/kg	Droperidol, μg/kg	Age Min, yr	Age Max, yr	Ondansetron + Droperidol n	Ondansetron + Droperidol POV	Placebo n	Placebo POV	Odds Ratio [95% Credibility Interval] after Inclusion of This Trial
Shende[13]	2001	Strabismus	0.15	25	1	15	60	8	60	38	0.10 [0.04–0.23]

Study	Year	Surgery	Ondansetron, mg/kg	Dexamethasone, mg/kg	Age Min, yr	Age Max, yr	Ondansetron + Dexamethasone n	Ondansetron + Dexamethasone POV	Placebo n	Placebo POV	Odds Ratio [95% Credibility Interval] after Inclusion of This Trial
Bhardwaj[14]	2004	Strabismus	0.15	0.2	2	12	30	3	39	20	0.12 [0.03–0.43]

n = number of children in the group; POV = number of children presenting the postoperative endpoint.

Table 14. Measure of Effectiveness of All Treatments

	Odds Ratio, Mean [95% Credible Interval]	Relative Risk, Mean [95% Credible Interval]
Ondansetron (0.1–0.15 mg/kg) *vs.* placebo	0.37 [0.35–0.39]	0.54 [0.51–0.56]
Tropisetron (0.1–0.2 mg/kg) *vs.* placebo	0.17 [0.13–0.22]	0.41 [0.34–0.50]
Dolasetron (0.35 mg/kg intravenous or 1.8 mg/kg oral) *vs.* placebo	0.16 [0.09–0.27]	0.39 [0.25–0.56]
Granisetron (0.040 mg/kg) *vs.* placebo	0.16 [0.10–0.20]	0.31 [0.20–0.45]
Dexamethasone (0.050–1.0 mg/kg) *vs.* placebo	0.31 [0.28–0.34]	0.53 [0.49–0.56]
Droperidol (5–25 μg/kg) *vs.* placebo	0.48 [0.37–0.61]	0.62 [0.52–0.74]
Ondansetron plus dexamethasone *vs.* ondansetron 0.050 mg/kg ondansetron + 0.150 mg/kg dexamethasone or 0.150 mg/kg ondansetron + 0.2 or 1.0 mg/kg dexamethasone	0.25 [0.20–0.31]	0.33 [0.27–0.40]
Tropisetron (0.1 mg/kg) plus dexamethasone (0.15 or 0.5 mg/kg) *vs.* tropisetron	0.31 [0.20–0.49]	0.49 [0.34–0.67]
Dolasetron (0.5 mg/kg) plus dexamethasone (1.0 mg/kg) *vs.* dexamethasone	0.29 [0.13–0.67]	0.48 [0.25–0.82]
Ondansetron (0.15 mg/kg) plus droperidol (25 μg/kg) *vs.* placebo	0.09 [0.04–0.23]	0.22 [0.10–0.45]
Ondansetron (0.15 mg/kg) plus dexamethasone (0.2 mg/kg) *vs.* placebo	0.12 [0.03–0.44]	0.22 [0.07–0.61]
Granisetron (0.040 mg/kg) plus dexamethasone (0.150 mg/kg) *vs.* placebo	0.05 [0.001–0.31]	0.10 [0.02–0.47]
Ondansetron plus dexamethasone *vs.* placebo extrapolated by indirect comparison		0.17 [0.14–0.21]
Tropisetron plus dexamethasone *vs.* placebo extrapolated by indirect comparison		0.20 [0.14–0.30]
Dolasetron plus dexamethasone *vs.* placebo extrapolated by indirect comparison		0.21 [0.12–0.39]

Statistical Analysis

We subjected the studies to a Bayesian analysis, with respect to the outcome reported, in a sequence that paralleled their dates of publication. Because many readers are probably unfamiliar with the methodology of Bayesian analysis, we provide an explanation of the method, kept as practical as possible, in appendix 1.

Based on the Bayes theorem, a posterior probability was calculated after inclusion of the data from the successive studies, to update a prior probability existing before inclusion of that study. For the first computation, for inclusion of the data from the first study, we used a noninformative prior probability, with a log odds ratio (OR) mean equal to 0 and an SD of the distribution of ORs equal to 10. This gives a flat distribution of the probabilities at this point and gives an equal probability to either treatment being superior to the other, given the absence of previous data, and starts the following comparisons from a neutral point of view. It is a 50/50 situation (log OR = 0 gives an OR = 1, and the SD of 10 means that 95% of the ORs values are between 0.0094 and 406.4207) and allows starting from a neutral standpoint. This is also called an uninformative prior. Thereafter, the posterior for the preceding group of trials served as the prior for the subsequent trial.

The mean log OR and the SD of the log ORs obtained at the end of the analysis were transformed to an OR and 95% credibility interval. These ORs were transformed to RRs by using the method of Zhang and Yu.[59]

The baseline risks (BLRs) of 70, 55, 30, and 10% described for the various risk categories on the pediatric risk scale[2] were updated using the computed RR in the formula (BLR − (BLR × (1 − RR))).

Two RRs were used that formed the upper and lower border of the 95% credibility interval. This resulted in a most optimistic value (using the lower border of the interval) and a most pessimistic value (using the upper border of the interval). These represent the lowest and highest risk values that can be expected with a 95% probability when treating a child from a given BLR category.

For each single-drug treatment and for the ondansetron plus droperidol and the granisetron plus dexamethasone combinations tested against a placebo, the procedure described was straightforward.

For the combination treatments that were not tested against a placebo (ondansetron plus dexamethasone, tropisetron plus dexamethasone, and dolasetron plus dexamethasone), an RR and 95% credible interval was computed against the single drug tested, using the same methodology as described for a single-drug treatment. Thereafter, an indirect comparison method, as suggested by Bucher *et al.*,[60] was used to extrapolate the RR of the combination against a placebo; this allowed calculation of a posttreatment risk using the same method as for the single-drug treatments.

The equations used for all calculations are given in appendixes 1 and 2.

All computations were made using the software program Lotus 1-2-3 97 Edition (IBM, Armonk, NY).

Results

The endpoints used in all of the included trials are given in table 1. The wording used is taken verbatim from the original article and is not our interpretation. The third column reports emetic symptoms that were explicitly not considered as an endpoint; the word *no* means simply that no exclusion is explicitly reported by the authors in the methodology section. The last column reports specific exclusion or inclusion criteria.

Vomiting is almost uniformly reported, with retching specifically included in more than half of the trials; however, in 6 trials, retching is explicitly not counted as an endpoint. Many studies also report some sort of chil-

Table 15. Expected Incidence of Postoperative Vomiting, by Risk Category, with All Treatments

Baseline Risk, %	Ondansetron	Tropisetron	Granisetron	Dolasetron	Dexamethasone	Droperidol	Ondansetron + Dexamethasone
Most optimistic effect							
70	35.7	23.8	14.0	17.5	34.3	36.4	8.4
55	28.1	18.7	11.0	13.8	27.0	28.6	6.6
30	15.0	10.2	6.0	7.5	14.7	15.6	3.6
10	5.1	3.4	2.0	2.5	4.9	5.2	1.2
Most pessimistic effect							
70	39.2	35	31.5	39.2	39.2	51.8	17.5
55	30.8	27.5	24.7	30.8	30.8	40.7	13.8
30	16.8	15	13.5	16.8	16.8	22.2	7.5
10	5.6	5	4.5	5.6	5.6	7.4	2.5

dren exclusion usually connected with recent treatment or occurrence of some sort of emetic symptom. Six trials report specifically excluding children with motion sickness and/or a history of postoperative vomiting.

The analysis of all the included trials are given in tables 2–13, including year of publication, the doses used, the type of surgery, the age of the children included, the number of children included in each group, and the number of children presenting the postoperative endpoint (called postoperative vomiting [POV] in the tables) in the group. The final column gives the mean ORs and their 95% credibility intervals resulting from the calculations after inclusion of each trial in the analysis.

The last OR is considered as the result obtained with the treatment in question. Tables 2 and 3 show the analysis for the trials with ondansetron compared with placebo; they list all of the intermediate logarithmic results to highlight the details of the methodology used.

The final ORs for all the treatments, and their transformation into RRs with their 95% credibility intervals, are given in table 14. Using the boundaries for these credibility intervals, the highest and lowest incidences expected with each treatment are given in table 15.

It seems that globally, the combination treatments result in lower RRs, and thus lower expected risks, than the single-drug treatments. When one considers the most pessimistic expectations, the best single-drug prophylaxis with the 5-hydroxytryptamine receptor antagonists and dexamethasone result in a 50–60% RR reduction. The results with droperidol offer a decrease of only approximately 40%.

It is also clear that the smallest credibility intervals, resulting in the smallest difference between the most optimistic and pessimistic stands, are obtained with ondansetron and dexamethasone; this can be attributed to the fact that these treatments were studied in the greatest number of trials, and the effect is thus known with the best precision.

With the combinations of a 5-hydroxytryptamine receptor antagonist and dexamethasone, one can expect an RR reduction of approximately 80%.

Sensitivity Analysis

However, in all of the published trials including only children, none concluded with a superiority of the placebo or the single-drug comparator. The study drug was statistically significantly better in all but 6 trials, which showed a strong but nonsignificant superiority of the study drug. This raises the possibility of a publication bias.

Using our method of calculation, a potential bias can be taken into account by changing the initial value of the prior, to take a more skeptic stand at the beginning of the analysis (appendix 3). In our case, the obvious choice seems to be to take as the initial probability the values reported in the trials with adult patients,[54,61] reporting an RR reduction of approximately half of the values we just reported.

Table 16 reports the values computed at the end of our reanalysis for the drug treatments for which we were able to find this appropriate prior probability. The results obtained for ondansetron and dexamethasone are nearly identical to those obtained with the noninformative prior, showing that with sufficient data available, the end results remains strongly in favor of this important effect. The other treatments, however, were unable to overcome this computational handicap. The expected incidences of postoperative vomiting using these skeptical priors are listed in table 17.

Discussion

Two key elements can be concluded from our results. The first one is that the RR reduction measured in children is approximately double that reported in adult patients, with all categories of drugs. This could indeed seem to be an unlikely increase in efficiency, and indeed the responsibility of a publication bias cannot be totally excluded; nevertheless, even after correction for this possibility, the magnitude of the therapeutic effect size was almost unchanged for ondansetron and dexamethasone. The second point is that with a treatment combining a 5-hydroxytryptamine receptor antagonist and dexamethasone or droperidol, an RR reduction of approximately 80% can be expected.

Table 15. Continued

Ondansetron + Droperidol	Tropisetron + Dexamethasone	Dolasetron + Dexamethasone	Granisetron + Dexamethasone
7	11.2	5.6	1.4
5.5	8.8	4.4	1.1
3	4.8	2.4	0.6
1	1.6	0.8	0.2
31.5	17.5	30.8	39.9
24.8	13.8	24.2	25.8
13.5	7.5	13.2	14.1
4.5	2.5	4.4	4.7

Although there is some overlap between the 95% credibility intervals for some single-drug and some combination treatments, overlap occurs essentially between treatments that have the widest 95% credibility intervals; these are the treatments with the smallest number of trials and patients. For the treatments with smaller 95% credibility intervals, ondansetron, tropisetron, and dexamethasone, there is no overlap when compared with ondansetron plus dexamethasone or tropisetron plus dexamethasone.

As stated before, the calculations for all the single-drug treatments and for the ondansetron plus droperidol combination are straightforward because they were compared with placebo. The other combinations were compared with single-drug treatments, and therefore, to be able to make a statement about their effect compared with placebo, we had to resort to the extra step of making an indirect comparison.

Indirect comparisons usually, but not always, agree with the results of head-to-head randomized trials. The only requirement is that the magnitude of the treatment effect is constant across differences in the populations' baseline characteristics. When there is no or insufficient

Table 16. Measure of Effectiveness of Treatments, Using a Skeptical Initial Prior Probability (Sensitivity Analysis)

	Odds Ratio, Mean [95% Credible Interval]	Relative Risk, Mean [95% Credible Interval]
Ondansetron (0.1–0.15 mg/kg) *vs.* placebo	0.38 [0.36–0.40]	0.55 [0.52–0.57]
Tropisetron (0.1–0.2 mg/kg) *vs.* placebo	0.43 [0.35–0.51]	0.73 [0.67–0.79]
Dolasetron (0.35 mg/kg intravenous or 1.8 mg/kg oral) *vs.* placebo	0.61 [0.49–0.76]	0.84 [0.77–0.92]
Granisetron (0.040 mg/kg) *vs.* placebo	0.61 [0.50–0.75]	0.78 [0.70–0.87]
Dexamethasone (0.050–1.0 mg/kg) *vs.* placebo	0.33 [0.31–0.37]	0.56 [0.52–0.59]
Droperidol (5–25 μg/kg) *vs.* placebo	0.59 [0.49–0.71]	0.72 [0.64–0.81]
Ondansetron plus dexamethasone *vs.* ondansetron	0.29 [0.23–0.36]	0.38 [0.31–0.45]
Ondansetron plus dexamethasone *vs.* placebo by indirect comparison		0.21 [0.15–0.28]
Computation of the Initial Prior Probabilities Used for Starting the Bayesian Analysis (Appendix 3)		
Ondansetron	Data from reference 61—OR [95% CI]: 0.64 [0.57–0.72] Maximum expected decrease is 0.43—No expected increase in risk Log OR = −0.272, SD log OR = 0.139 (corresponding to a 95% credible interval for the OR of 1.14–2.0)	
Tropisetron	Data from reference 54—OR [95% CI]: 0.70 [0.61–0.81] Maximum expected decrease is 0.39—No expected increase in risk Log OR = −0.247, SD log OR = 0.126 (corresponding to a 95% credible interval for the OR of 1.56–2.0)	
Dolasetron	Data from reference 54—OR [95% CI]: 0.72 [0.62–0.83] Maximum expected decrease is 0.38—No expected increase in risk Log OR = −0.239, SD log OR = 0.122 (corresponding to a 95% credible interval for the OR of 1.24–2.0)	
Granisetron	Data from reference 54—OR [95% CI]: 0.71 [0.64–0.79] Maximum expected decrease is 0.36—No expected increase in risk Log OR = −0.223, SD log OR = 0.114 (corresponding to a 95% credible interval for the OR of 1.68–2.0)	
Dexamethasone	Data from reference 61—OR [95% CI]: 0.63 [0.56–0.71] Maximum expected decrease is 0.44—No expected increase in risk Log OR = −0.920, SD log OR = 0.148 (corresponding to a 95% credible interval for the OR of 1.12–2.0)	
Droperidol	Data from reference 61—OR [95% CI]: 0.66 [0.58–0.74] Maximum expected decrease is 0.42—No expected increase in risk Log OR = −0.272, SD log OR = 0.139 (corresponding to a 95% credible interval for the OR of 1.16–2.0)	
Ondansetron plus dexamethasone	Data from table 16—OR [95% CI]: 0.38 [0.36–0.40] Maximum expected decrease is 0.64—No expected increase in risk Log OR = −0.511, SD log OR = 0.261 (corresponding to a 95% credible interval for the OR of 0.72–2.0)	

CI = confidence interval; log OR = natural logarithm of the odds ratio; OR = odds ratio; SD log OR = SD of the distribution of the natural logarithm of odds ratios.

Table 17. Expected Incidence of Postoperative Vomiting, by Risk Category, Computed from the Results Obtained Using a Skeptical Prior Probability

Baseline Risk, %	Ondansetron	Tropisetron	Granisetron	Dolasetron	Dexamethasone	Droperidol	Ondansetron + Dexamethasone
Most optimistic effect							
70	36.4	39.9	49.0	53.9	36.4	44.8	10.5
55	28.6	31.3	38.5	42.3	28.6	35.2	8.2
30	15.6	17.1	21.0	23.1	15.6	19.2	4.5
10	5.2	5.7	7.0	7.7	5.2	56.4	1.5
Most pessimistic effect							
70	39.9	55.3	60.9	64.4	41.3	56.7	19.6
55	31.3	43.4	47.8	50.6	32.4	44.5	15.4
30	17.1	23.7	26.1	27.6	17.7	24.3	8.4
10	5.7	7.9	8.7	9.2	5.9	8.1	2.8

direct evidence from randomized trials, the adjusted indirect comparison may provide useful or supplementary information on the relative efficacy of competing interventions.[62,63] The validity of the adjusted indirect comparisons depends on the internal validity and similarity of the included trials. In the case of ondansetron plus dexamethasone, we have a single study against placebo. The 95% credibility intervals for this study did overlap with the results obtained from indirect comparison, but it must nevertheless be noted that the 95% credibility interval for this study is so large that the probability of overlapping is great, in the absence of an enormous difference that would probably be generated from large differences in the studied populations.

From a practical point of view, the results in table 14 can serve as a guide for performing a cost-effectiveness evaluation. The prices of all the drugs and the financing from the various health insurance systems vary greatly across the world. For example, postoperative vomiting has been reported as a main reason for unplanned overnight hospital admission.[64] A cost effectiveness calculation taking into account the local expenses related to the drugs and the eventual hospital admission can be balanced for each risk category described on the pediatric risk scale; it could seem that for certain low-risk patients, only single-drug prophylaxis is cost-effective.

Our final results expressed in absolute percentage of vomiting depend, of course, of the incidences ascribed to each category of the pediatric risk scale, which is not without weaknesses. Some questioning about this scale was already published, because age older than 3 yr and surgery for more than 30 min (two of the four risk markers) were not found to be markers of increased risk in a recent study.[58] However, the ORs and RRs that we computed are independent of this risk scale and can always be used with different BLR values. One can even use values from his or her own practice and the results from table 14 to calculate the expected incidence with the various treatments.

Table 18. Comparison of Relative Risks from the Current Analysis with Relative Risks for Vomiting from the Cochrane Review

	From the Current Analysis, Mean [95% Credible Interval]	From the Cochrane Review,[54] Mean [95% Confidence Interval]
Ondansetron	0.54 [0.51–0.56]	0.55 [0.50–0.59]
Tropisetron	0.41 [0.34–0.50]	0.59 [0.50–0.69]
Dolasetron	0.39 [0.25–0.56]	0.63 [0.51–0.69]
Granisetron	0.31 [0.20–0.45]	0.41 [0.28–0.59]*
Dexamethasone	0.53 [0.49–0.56]	0.51 [0.46–0.57]
Droperidol	0.62 [0.52–0.74]	0.65 [0.46–0.57]

* Results recalculated (using classical meta-analysis) from the data in the Cochrane review[54] without the 39 trials from Fujii *et al.* listed on pages 297–9 in the Cochrane review.[54]

Another problem arising from all of these studies in children is the variability of the endpoint (the description of the actual emetic events counted), as well as of the inclusion and exclusion criteria (table 1). This probably results in underreporting of emetic events because of the exclusion of retching in certain trials and the absence of counting nausea in most studies, even if this could have been reported by the older children. The effect of excluding the children with a history of postoperative vomiting or motion sickness or a recent emetic event could have as a consequence exclusion of the children with the highest risk from many trials, a consequence whose influence on our results can only be speculative.

This underreporting could also partly account for the increased efficiency of the treatments in children, because in adults a large portion of postoperative nausea and vomiting is in fact nausea. In the study of Apfel *et al.*,[61] which served as our reference in adults for ondansetron, dexamethasone, and droperidol, all emetic symptoms (vomiting, retching, and nausea) were counted as an event. This could be the case, because it seems that when taking the results from table 1 in the Cochrane review,[54] the RR after treatment was lower for vomiting than for nausea, and the results for ondansetron, dexamethasone, and droperidol are similar to those obtained in our current analysis (table 18).

As a whole, it seems that the expected incidences values in table 15 are usually very close to measured incidences in the trials, but that sometimes (as for the tropisetron[65] and tropisetron plus dexamethasone treatments) they seem to predict lower incidences that those measured. But it is also difficult to verify the accuracy of predictions with data that were in fact used to produce the statistical model, with the

exception of the studies from Kim *et al.*[58] and Gross *et al.*[65] On the other hand, the ORs and RRs in table 14 could represent accurately the effectiveness of the treatments, but the BLRs in some studies were not similar to those reported in the pediatric risk score.[2]

Appendix 1

The Bayesian paradigm considers that the role of data is to update our knowledge of a question under scrutiny that is considered as a parameter of interest in a statistical model.

In our case, the parameter of interest is the odds ratio.

Therefore, a fundamental feature of Bayesian analysis is the incorporation of prior information about the parameter of interest. The Bayes theorem gives a simple and uncontroversial result in probability theory, relating probabilities of events before (the "prior" in Bayesian parlance) and after an experiment (the "posterior" in Bayesian parlance).

Therefore, the prior information, expressed as a probability distribution for the parameter of interest, represents what is known before the data are taken into account; the data are expressed as a probability distribution known as the likelihood function, which demonstrates the degree of support from the data for the various possible values of the parameter of interest. The likelihood function is integrated with the prior to produce the posterior distribution, which represents our updated knowledge of the parameter of interest, given the data.

Following the work of Spiegelhalter *et al.*,[66] we use normal distributions to summarize the information about the odds ratios on the natural log scale. The Bayesian inference supports direct statements about the probability of the magnitude of an effect, and therefore the 95% credibility interval means exactly what it is supposed to, *i.e.*, that there is a 95% probability that the real value of the odds ratio lies between the two borders.

Another advantage offered from our calculation methodology is the ease in updating the current data. Additional trials can be added easily to the analysis to provide a new evaluation of the expected efficacy.

Computational Methodology

This appendix highlights the methodology used to compute the odds ratio and the relative risk, derived from the Bayes theorem, representing the effectiveness of a treatment.

The equations are not presented in a general mathematical form, but show the particularities and use a naming convention adapted to the situation of analyzing trials expressed as a number of events in a "treated group" and a "control group."

Once a first logarithm of posterior odds ratio, with its SD, is obtained as explained below, these values serve as prior for the calculation after inclusion of the data of the next study (see table 3 for application of the method). This mechanism is repeated until inclusion of all trials.

This methodology is best understood by integrating these explanations with the intermediate results listed in table 3 as an example.

E_T = number of patients with event in treated group
noE_T = number of patients without event in treated group
n_T = number of patients in treated group
E_C = number of patients with event in control group
noE_C = number of patients without event in control group
n_C = number of patients in control group
OR_d = odds ratio from the data
$var(OR_d)$ = variance of the distribution of odds ratios
$SD(OR_d)$ = SD of the distribution of odds ratios
log OR_d = natural logarithm of odds ratio from the data

$$OR_d = \frac{(E_T + 0.5) \times (noE_C + 0.5)}{(E_C + 0.5) \times (noE_T + 0.5)}$$

$$var(OR_d) = \frac{1}{(E_T + 0.5)} + \frac{1}{(E_C + 0.5)} + \frac{1}{(noE_T + 0.5)} + \frac{1}{(noE_C + 0.5)}$$

$$SD(OR_d) = \sqrt{var(OR_d)}$$

$$\log OR_d = \ln OR_d$$

Computation of the Natural Logarithm of the Posterior Odds Ratio

$logOR_p$ = natural logarithm of the prior odds ratio
$SD(logOR_p)$ = SD of the distribution of the natural logarithm of prior odds ratios
$var(logOR_p)$ = variance of the distribution of the natural logarithm of prior odds ratios
$var(logOR_p) = (SD(logOR_p))^2$
logOR = natural logarithm of posterior odds ratio
SD(logOR) = SD of the distribution of the natural logarithm of the posterior odds ratios

$$A = \frac{0.5 \times \log OR_d}{var(OR_d)}$$

$$B = \frac{0.5}{var(OR_d)} + \frac{0.5}{var(\log OR_p)}$$

$$C = \frac{0.5 \times \frac{\log OR_p}{var(\log OR_p)}}{\frac{0.5}{var(OR_d)} + \frac{0.5}{var(\log OR_p)}}$$

$$\log OR = \frac{A}{B} + C$$

$$SD(\log OR) = \frac{1}{\sqrt{\frac{1}{var(OR_d)} + \frac{1}{var(\log OR_p)}}}$$

Transform to a Posterior Odds Ratio

$$OR = e^{\log OR}$$

95% Credibility Interval of Odds Ratio

$$e^{\log OR \pm (1.96 \times SD(\log OR))}$$

Transform Odds Ratios to Relative Risks (RRs)

$$RR = \frac{OR}{\left(1 - \frac{E_C}{n_C}\right) + \left(\frac{E_C}{n_C} \times OR\right)}$$

Appendix 2

Indirect Comparison

Relative risk of single-drug treatment *versus* placebo: $RR_{S/PBO}$
Relative risk of combination *versus* single-drug treatment: $RR_{C/S}$
Relative risk of combination treatment *versus* placebo: $RR_{C/PBO}$

$$RR_{C/PBO} = RR_{S/PBO} \times RR_{C/S}$$

Calculation of the 95% Credibility Interval

The variance of the natural logarithm of a relative risk is calculated as

$$\mathrm{var}(\log \mathrm{RR}) = \left[\frac{\log(\mathrm{ub}) - \log(\mathrm{lb})/2}{1.96}\right] \times \left[\frac{\log(\mathrm{ub}) - \log(\mathrm{lb})/2}{1.96}\right],$$

where ub = upper border of the 95% credibility interval and lb = lower border of the 95% credibility interval.

This allows the calculation of

The variance of the natural logrithm of $RR_{S/PBO}$:

$$\mathrm{Var}[\log(RR_{S/PBO})] \quad (1)$$

The variance of the natural logrithm of $RR_{C/S}$:

$$\mathrm{Var}[\log(RR_{C/S})] \quad (2)$$

by using the upper and lower borders of the 95% credibility intervals that can be found in table 14.

From (1) and (2),

$$\mathrm{var}[\log(RR_{C/PBO})] = \mathrm{var}[\log(RR_{S/PBO})] + \mathrm{var}[\log(RR_{C/S})] \quad (3)$$

From (3), the 95% credibility interval for $RR_{C/PBO}$ can be calculated as

$$e^{[\log(RR_{C/PBO}) \pm 1.96\sqrt{\mathrm{var}(\log RR_{C/PBO})}]}.$$

Appendix 3

In the current situation, an interesting feature of the Bayesian techniques can be use to tackle the two obvious problems that appear at the end of our initial analysis. The first is the size of the risk reduction, which is approximately double what is reported in adult patients. The second problem is the possibility of facing a publication bias.

Skepticism about large treatment effects can be formally expressed and used in interpretation of results that cause surprise. Rarely in medicine is there a situation where we know absolutely nothing about the probability of a treatment to succeed and are therefore only able to use a noninformative prior.

For the current analysis, we have a vast amount of data in adult patients from which we can make an initial informed guess of the likely therapeutic effect.

This is done by computing a prior probability ("prior") than can serve as the initial value at the start of the Bayesian analysis; this makes it much harder to find a large effect of the treatment. The computational mechanism of our Bayesian meta-analysis is influenced by the size of the SD of the distribution of the natural logarithm of the odds ratios: the smaller the size, the bigger the skepticism expressed.

This is the formal way of introducing a skeptical view on the initial (and maybe too good) results. If, despite this "handicap," the end results of our initial analysis can be (or can almost be) repeated, this is a strong indication that indeed, the results can be as extreme as those we obtained initially.

Starting a Bayesian analysis with different priors is called a sensitivity analysis, and shows how a result can be influenced by an initial belief before even beginning a study. Of course, with sufficiently strong data, the clinical conclusion should be the same with any reasonable initial prior probability.

The following section shows how to compute a prior based on values of maximal expected risk decrease and increase that are taken from the existing literature (in our case, the data on adult patients).

The results from this analysis and the data on which we have performed these computations are shown in table 16.

Computation of the Mean and SD for a 95% Confidence Interval of the Associated Normal Distribution with All Possible Values of the Odds Compatible with One's Belief

A = maximal expected decrease in odds ratio (if 15%, use 0.85)
B = maximal expected increase in odds ratio (if 15%, use 1.15)
Log(A) = natural logarithm of A
Log(B) = natural logarithm of B
log OR = natural logarithm of mean odds ratio
SD(log OR) = SD of the distribution of the natural logarithm of the odds ratios

$$\log \mathrm{OR} = \frac{\log(\mathrm{A}) + \log(\mathrm{B})}{2}$$

$$\mathrm{SD}(\log \mathrm{OR}) = \frac{|\log(\mathrm{A})| + |\log(\mathrm{B})|}{3.92}$$

These values are used as the initial prior probabilities to begin the Bayesian meta-analysis.

In table 16, the maximal expected decrease in odds ratio corresponds to the lower bound of the 95% confidence interval for the odds ratio computed from the data in references 54 and 61. It was also hypothesized that there was no increase in risk to be expected with the administration of the treatment.

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