

Propofol anaesthesia and postoperative nausea and vomiting: quantitative systematic review of randomized controlled studies

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Summary

We have analysed randomized controlled studies which reported the incidence of postoperative nausea and vomiting (PONV) after propofol anaesthesia compared with other anaesthetics (control). Cumulative data of early (0–6 h) and late (0–48 h) PONV were recorded as occurrence or non-occurrence of nausea or vomiting. Combined odds ratio and number-needed-to-treat were calculated for propofol as an induction or maintenance regimen, early or late outcomes, and different emetic events. This was performed for all control event rates and within a range of 20–60% control event rates. We analysed 84 studies involving 6069 patients. The effect of propofol on PONV was dependent mainly on the method of administration, time of measurement and range of control event rates. When all studies were included the number-needed-to-treat to prevent PONV with propofol was more than 9 when used for induction of anaesthesia and at best 6 when used for maintenance. Within the 20–60% control event rate range, best results were achieved with propofol maintenance to prevent early PONV: the number-needed-to-treat to prevent early nausea was 4.7 (95% confidence interval 3.8–6.3), vomiting 4.9 (4–6.1) and any emetic event 4.9 (3.7–7.1). Within the 20–60% control event rate, of five patients treated with propofol for maintenance of anaesthesia, one will not vomit or be nauseated in the immediate postoperative period who would otherwise have vomited or been nauseated. This may be clinically relevant. In all other situations the difference between propofol and control may have reached statistical significance but was of doubtful clinical relevance. Treatment efficacy should be established within a defined range of control event rates for meaningful estimates of efficacy and for comparisons. (*Br. J. Anaesth.* 1997; **78**: 247–255).

Key words

Anaesthetics i.v., propofol. Vomiting, nausea. Vomiting, antiemetics. Vomiting, incidence. Statistics.

Propofol is thought to be antiemetic and therefore useful to decrease the incidence of postoperative nausea and vomiting (PONV).^{1–3} However, the mechanism of its effect on PONV is obscure. Interpretations range from propofol being less

emetogenic than other anaesthetics⁴ to being directly antiemetic.² When given in subanaesthetic doses after surgery either as prophylaxis^{5,6} or as treatment,² results were contradictory.

A biological basis for propofol being an antiemetic is lacking. In animals, propofol did not interact strongly with dopamine D2 receptors⁷ and in human volunteers subhypnotic doses of propofol did not prevent vomiting induced by the dopamine agonist apomorphine.⁸ These data make it unlikely that propofol has a significant antiemetic effect via dopamine receptors.⁹ Results from *in vitro* studies were inconclusive.^{10,11} One *in vitro* model suggested that propofol had little or no effect on endogenous 5-HT₃ receptors while volatile anaesthetics enhanced 5-HT₃ receptor-mediated currents.¹⁰ This may be indirect evidence that propofol has less emetogenic potency than other anaesthetics.¹⁰ In another *in vitro* study propofol was shown to be a potent 5-HT₃ receptor blocker.¹¹ However, in this experiment all of the general anaesthetics examined caused concentration-dependent inhibition of the 5-HT₃ channel.¹¹ Other vague theoretical mechanisms of propofol and antiemesis include direct depressant action on the chemoreceptor trigger zone, vagal nuclei and other centres implicated in nausea and vomiting,⁷ or modulation of some subcortical pathways.² Although documented anecdotally, propofol-induced improvement of mood and well-being could not be reproduced in a randomized experimental human study.¹²

The evidence is that propofol has only a minimal effect on vomiting in paediatric strabismus surgery, a clinical situation with a particularly high risk of PONV.¹³ The aim of this meta-analysis was therefore to test the evidence that propofol, when used for induction or maintenance of anaesthesia, decreases the incidence of PONV compared with other anaesthetic techniques.

Methods

MEDLINE (Knowledge Server v3.25) was searched (1981 to December 1995) for randomized

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controlled studies which evaluated the effect of propofol compared with other anaesthetics (control) on PONV and reported the outcome in dichotomous form (number of patients with and without an outcome). The search strategy was not restricted to the English language and used combinations of the free text terms emesis, nausea, vomiting, adverse effects (subheading), and propofol, Disoprivan, Diprivan, Disopropofol or ICI35868. Additional reports were identified from reference lists of retrieved reports and from review articles of PONV and propofol. Unpublished studies were not sought. Abstracts were not considered. Reports without randomization or with an inadequate method of randomization (such as patient's date of birth) were excluded from analysis.

Information on patients, anaesthetics, surgery and definition of PONV was obtained from each report. Three different PONV outcomes were extracted in dichotomous form: nausea, vomiting (including retching), and any emetic event (nausea, vomiting or nausea and vomiting). These outcomes were treated separately as "emetic events". Incidences of early (0–6 h) and late (0–48 h) emetic events were extracted. Thus a maximum of three different emetic events could be extracted from each study, both early and late. When several incidences of events were reported at different times the cumulative values nearest to 6 and 48 h after operation were analysed. Emetic events "during recovery" or "after operation" were considered as early data. No weighting was used for different grades of nausea, number of vomiting episodes, time to first vomiting episode, number of patients needing antiemetic rescue medication, delay until discharge or scores of patient satisfaction.

When propofol was used only for induction it was compared with other i.v. or inhalation induction techniques. Propofol as a maintenance anaesthetic was compared with other maintenance regimens. When multiple comparisons were possible between propofol and several other anaesthetics in one study, only one control arm was analysed. The primary choice for control was, for induction, another i.v. agent and for maintenance, an inhalation method. Comparisons where propofol was used as an induction agent in both active and control groups were excluded. Comparisons between a nitrous oxide-free propofol arm (total i.v. anaesthesia) and a nitrous oxide-based control arm were not considered because of the potential effect of nitrous oxide on emesis.¹⁴ However, studies were analysed when nitrous oxide was omitted in both the propofol and control arms.

The plot of L'Abbé, Detsky and O'Rourke¹⁵ of event rates with propofol compared with control event rates was used as a graphical means of exploring the efficacy of propofol and homogeneity of the data set. A scatter predominantly lying between the line of equality and the control axis suggested efficacy with propofol and homogeneity.

Statistical significance and clinical relevance of the efficacy of propofol were evaluated using odds ratio and number-needed-to-treat (NNT)¹⁶ methods. Odds ratio estimates were calculated with 95% confidence intervals (95% CI) using a fixed effects

model.¹⁷ Point estimates and 95% CI of the NNT were calculated.¹⁸ The NNT indicated how many patients had to be exposed to propofol in order to prevent one particular emetic event in one of them, who would have had this emetic outcome with a control treatment (that is, with another anaesthetic).

Efficacy was defined as absence of an emetic event. The efficacy of propofol was analysed separately for different modes of administration (induction, maintenance), different times (early, late emetic events) and different emetic events (nausea, retching/vomiting, any emetic event). This was done by combining single propofol or control arms both independent of control event rates (i.e. for all incidences of emetic events with control anaesthetics) and within a range of 20–60% control event rates (i.e. after exclusion of all data from studies with a control event rate less than 20% or greater than 60%). This range of control event rates was a *post hoc* definition.

Absence of a statistically significant improvement of propofol over control was assumed when the lower 95% confidence limit of the odds ratio was <1 or when the NNT point estimate was either negative or its upper 95% confidence limit included no effect (an infinite NNT). For simplification, only NNT with 95% CI are shown. Our arbitrary definition of a clinically relevant effect for prophylaxis of PONV was an NNT ≤5. An NNT of 5 would be the best estimate of efficacy which could be achieved with a control event rate of 20%.

Calculations were performed using Excel v 4.0 on a Power Macintosh 7100/66. Tables with data extracted from the analysed reports, including odds ratios with confidence limits, are available from the world-wide-web (<http://www.jr2.ox.ac.uk/Bandolier/painres/propoponv.html>).

Results

We considered 122 reports for analysis; 19 were excluded because propofol was used for induction in the control group (11 studies) and/or because nitrous oxide was omitted in the propofol but not in the control group (eight studies) and no other comparisons were possible. Another 19 studies were excluded for various reasons; six were not randomized,^{19–24} the randomization method was inadequate in four,^{25–28} the technique of maintenance was not mentioned in two,^{29,30} three were not adequately controlled (opioid or droperidol only in one group),^{31–33} one had eltanolone as the only control arm³⁴ and data from three studies were published twice.^{35–40}

Data from 84 randomized controlled studies involving 6069 patients (3098 treated with propofol) were analysed. A list of these references is given in the appendix. Median group size was 22 (range 10–75) patients. Thirty-one (37%) studies were sponsored by the manufacturer of propofol. Propofol as an induction agent or as a maintenance regimen was compared with other anaesthetic techniques in a large variety of surgical settings in children and adults. Maintenance of anaesthesia with propofol included induction with propofol or an initial bolus of propofol in all studies.

Table 1 One control arm per emetic outcome and study. Nausea, vomiting (including retching), and any emetic event (nausea, vomiting, or nausea and vomiting) may be reported in one study. *(a) and (c) = number of patients in whom the event was absent; (b) and (d) = the total number of patients in the listed studies. Control event rate = Incidence of emetic outcomes in control group; CI = confidence interval; n/a = not applicable. Early events = 0–6 h; late events = 0–48 h; ∞ = infinity (negative value, indicating absence of a statistically significant difference between propofol and control). Odds ratios with 95% confidence limits are available from the internet (<http://www.jr2.ox.ac.uk/Bandolier/painers/propconv.html>)

Event	All control event rates				20–60% control event rates			
	Absence of given events		Number-needed-to-treat		Absence of given events		Number-needed-to-treat	
	With propofol a/b*	With control c/d*	(95% CI) the event with propofol 1/(c/d-a/b)	Reference	With propofol a/b*	With control c/d*	(95% CI) the event with propofol 1/(c/d-a/b)	Reference
Propofol for induction—early events								
Nausea	308/354	269/353	9.3 (6.1–19.4)	[65–77]	42/63	29/62	5.0 (2.7–35)	[68], [77]
Vomiting	360/415	329/414	13.7 (8.1–45.4)	[65–68], [70–81]	161/197	133/197	7.0 (4.4–17)	[67], [68], [75–80]
Any event	183/217	175/220	20.9 (8.3–∞)	[36], [82–87]	61/77	60/83	14 (5.0–∞)	[83], [86]
Propofol for induction—late events								
Nausea	81/101	79/101	50.1 (7.6–∞)	[73], [76], [80], [88]	48/65	45/64	28 (5.3–∞)	[73], [80], [88]
Vomiting	107/130	99/131	14.9 (6–∞)	[73], [76], [88–90]	62/81	54/81	10 (4.2–∞)	[73], [76], [88]
Any event	no data	no data	n/a		no data	no data	n/a	
Propofol for maintenance—early events								
Nausea	945/1064	790/1035	8 (6.4–10.8)	[40], [42–50], [53–56], [68], [73], [75], [77], [91–102]	418/507	310/506	4.7 (3.8–6.3)	[40], [42], [47], [50], [53–56], [68], [77], [91], [93–95], [97–100], [102]
Vomiting	1273/1339	1098/1304	9.2 (7.6–11.7)	[4], [38], [40–56], [68], [73], [75], [77–79], [93–99], [102–108]	559/608	410/575	4.9 (4.0–6.1)	[4], [40], [41], [43], [51–56], [68], [75], [77–79], [94], [95], [97], [102], [103], [107], [108]
Any event	399/440	311/417	6.2 (4.7–9)	[1], [82], [83], [87], [109–119]	237/263	187/269	4.9 (3.7–7.1)	[1], [83], [110], [112], [114], [116–119]
Propofol for maintenance—late events								
Nausea	209/228	171/230	5.8 (4.2–9.4)	[38], [73], [88], [96], [102], [120–123]	117/133	96/134	6.1 (3.9–14.5)	[73], [88], [121], [122]
Vomiting	277/346	245/349	10.1 (6.2–28.8)	[4], [38], [73], [88], [96], [102], [107], [108], [120], [122–125]	165/217	140/219	8.3 (4.9–28)	[4], [73], [88], [102], [107], [108], [122]
Any event	64/70	57/70	10 (4.7–∞)	[126], [127]	44/50	37/50	7.1 (3.4–∞)	[126], [127]

The event rate scatters (fig. 1) suggested improvement with propofol over control mainly for early outcomes when propofol was used for maintenance, and also suggested homogeneity for all data sets. The mean control event rate (incidence of PONV in controls) was 22% (range 0% to almost 70%). For all 84 randomized controlled studies a total of 169 different control event rates (nausea, vomiting or any emetic event) were reported; 77 (46% of all reported events) had an incidence less than 20% and six (4%) an incidence of more than 60%.

COMBINED ANALYSIS FOR ALL CONTROL EVENT RATES (TABLE 1)

For all control event rates the combined analysis indicated statistically significant results (NNT confidence interval excluding infinity) in favour of propofol for all three PONV outcomes only when propofol was used as a maintenance regimen and

only when early events were analysed. Under these conditions, 11–16% of patients (NNT 6.2 for absence of any emetic event, 8 for absence of nausea and 9.2 for absence of vomiting) undergoing propofol anaesthesia will not have an emetic event in the early postoperative period, who would have vomited or been nauseated with another anaesthetic.

When early and late outcomes after propofol as an induction agent or late outcomes after propofol maintenance were analysed, the combined NNT for all control event rates was always greater than 9 and, except for late absence of nausea after propofol maintenance, sometimes propofol was not significantly different from control.

ANALYSIS WITHIN THE RANGE OF 20–60% CONTROL EVENT RATES (TABLE 1, FIG. 1)

Within the 20–60% range of control event rates, the mean incidence of early and late PONV in controls

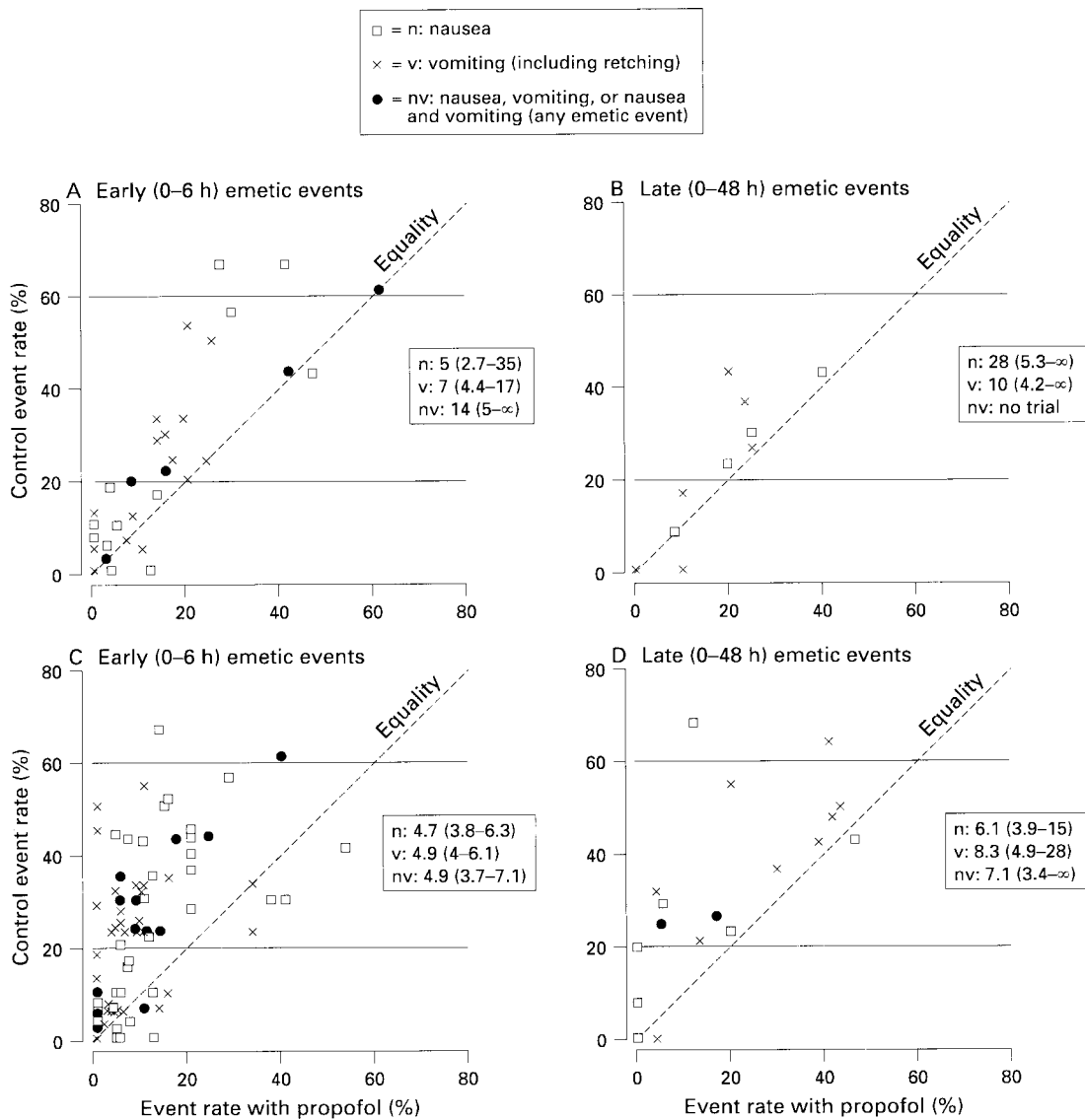


Figure 1 Early (A, C) and late (B, D) emetic event rates with propofol for induction (A, B) and maintenance (C, D) of anaesthesia compared with other anaesthetics (control). Three different emetic events (see key), both early and late, may be from one study. Only one control arm per study is considered. Horizontal lines indicate a range of control event rates of 20–60%. Values are number-needed-to-treat (95% confidence interval) to prevent an emetic event with propofol within this range. ∞=infinity (absence of a statistically significant difference between propofol and control).

was 36% and 32% when propofol was used for induction, and 33% for both times when propofol was used for maintenance.

Propofol induction (fig. 1A, B) was significantly better than control for absence of both early nausea and vomiting (NNT 5 and 6.7, respectively, each with wide confidence intervals). Absence of any emetic event in the early postoperative period after propofol induction was not significantly different from control. Late outcomes after propofol induction were either not significantly different from control or there were no studies reporting this outcome.

Propofol as a maintenance regimen (fig. 1C, D) was significantly better than control for all early emetic events; point estimates of the NNT to prevent early nausea, vomiting and any emetic event were approximately 5, with confidence intervals ranging from 4 to 7. Prevention of late vomiting and nausea with a propofol maintenance regimen had an NNT of approximately 8 and 6, respectively, both with wide confidence intervals, whereas prevention of late combined emetic events was not significantly different from control.

SUBGROUP ANALYSIS: TWO DIFFERENT SURGICAL SETTINGS

In 11 studies, propofol maintenance was compared with other anaesthetics in more than 1000 patients undergoing minor gynaecological surgery (abortion, curettage).^{41–51} The mean incidence of early vomiting without propofol was 10%; the NNT to prevent early vomiting with propofol was 16 (11–32).

In five studies of 200 patients undergoing major gynaecological surgery, including hysterectomy and laparoscopy,^{52–56} the mean incidence of early vomiting in controls was 32%; the NNT to prevent early vomiting with a propofol maintenance regimen compared with other anaesthetics was 4.2 (3–8).

Discussion

Two of the most recent comprehensive review articles on propofol stated that a significant decrease in PONV was observed with the use of propofol for anaesthesia,⁵⁷ and that an increasing body of literature supported the antiemetic activity of propofol.³ However, very few review articles use valid methods to identify, assess and synthesize information.⁵⁸

The main steps in our approach to propofol and PONV were to identify data systematically and without bias, to define homogeneous subgroups of clinical interest and to use quantitative methods of analysis which allowed sensible statistical and clinical conclusions to be drawn. Further, an arbitrary range of control event rates, excluding studies with very low or very high PONV incidences, enabled analysis of treatment efficacy within a set of data from studies with clinical validity. The lower boundary (control event rate 20%) was set because antiemetic prophylaxis was not considered to be worthwhile when the event rate without treatment was less than 20%. Moreover, in such a setting there would not be enough nausea or vomiting to allow sensitive assay of treatment efficacy. The upper

boundary (control event rate 60%) was set because a study which reported an incidence of nausea or vomiting in controls of more than 60% could not be considered as representative of clinical routine. Although a high incidence of vomiting may be reported in particular settings, such as paediatric strabismus surgery,¹³ this cannot be regarded as a representative cross-section of clinical reality. Audit has shown that the mean incidence of nausea and vomiting across different surgical settings is approximately 20–40%.^{59–62} When control event rates extend beyond this any intervention may become more or less effective and confound the combined results of a meta-analysis.

Within the 20–60% range, mean PONV incidences in controls were similar for early and late outcomes, and for propofol as an induction agent and maintenance regimen. Comparisons of efficacy could, therefore, be made between forms of administration (induction *vs* maintenance) and times (early *vs* late outcomes) without the danger of confounding the results because of different levels of control event rates.

What are the clinically relevant results of this meta-analysis? First, propofol anaesthesia should not be regarded as a universal prophylactic antiemetic if used non-selectively; too many patients would have to be treated with propofol in order to prevent PONV in one of them. A large number of studies and patients in a great variety of clinical settings were analysed; the risk of emetic outcomes without propofol when all studies were included was approximately 22%. This indicates that the data set was a representative cross-section of clinical routine rather than a selected subgroup of high-risk settings. Combined analyses for this data set, regardless of the control event rates, showed a clinically negligible effect of propofol on PONV compared with controls (number-needed-to-treat > 5) and sometimes the difference was not statistically significant. These results suggest that it may be inappropriate to expect a beneficial effect of propofol on PONV in every clinical situation.

Second, within the restricted range of control event rates (20–60%) propofol may decrease the incidence of PONV to a clinically relevant extent, but only when given as a maintenance regimen and only in the first few hours after surgery. Even in this setting five patients have to be treated with propofol to prevent early nausea or vomiting in one of them, who would have vomited or been nauseated with another anaesthetic. For late PONV this degree of benefit was lost; despite the same mean control event rate, point estimates of the NNT were higher than for early outcomes and confidence intervals were wide or included no benefit. These results suggest that propofol, when used for maintenance of anaesthesia, may produce a short-lived 20% reduction in vomiting and nauseated patients in a high-risk setting for emesis (i.e. control event rate 20–60%). These results also suggest that the effect of propofol on PONV does not influence long-term patient comfort. It is interesting to note in this connection that late emetic outcomes, although of undoubted importance,⁶³ were documented in only approximately

25–30% as many patients as early outcomes. This may be because of several factors. Anaesthetists may not be interested in late outcomes and may avoid the increased effort which is needed for prolonged follow-up of patients.

Third, although there is no way from our model to predict an individual patient's outcome with propofol, it may be possible to identify clinical subgroups with higher event rates and a corresponding greater efficacy with propofol. This was shown for paediatric strabismus surgery¹³ and confirmed in this study, because women undergoing major gynaecological interventions were much more likely to profit from the effect of propofol on PONV than those undergoing minor gynaecological surgery. Subgroup analysis may enable more rational decision making on how and when to use propofol in a particular group of patients to optimize any potential effect on PONV. This subgroup analysis also demonstrated that it is possible to identify clinical settings where a beneficial effect of propofol on PONV is unlikely.

Fourth, although suggested recently,⁶⁴ propofol as an induction agent cannot be regarded as worthwhile prophylaxis for PONV. The efficacy of propofol was either inconsistent or clinically irrelevant for early outcomes and not significantly different from control for late outcomes.

In conclusion, based on data from all published randomized, controlled studies there is evidence that propofol may have a clinically relevant effect on PONV, but only in the short term, when given as a maintenance regimen and when the event rate without prophylaxis is more than 20%. In all other situations—propofol for induction, late outcomes, low control event rates—the difference between propofol and control may be statistically significant but is clinically unimportant. It is over optimistic to expect propofol to act as an antiemetic in every clinical setting, especially if the event rate without prophylaxis is low.

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Appendix

ANALYSED RANDOMIZED, CONTROLLED STUDIES

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