

Meta-analytic comparison of prophylactic antiemetic efficacy for postoperative nausea and vomiting: propofol anaesthesia *vs* omitting nitrous oxide *vs* total i.v. anaesthesia with propofol

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Summary

Data from two published and one new meta-analysis were reviewed to compare the antiemetic efficacy of three different anaesthetic regimens: (i) propofol anaesthesia compared with another anaesthetic (control); (ii) anaesthesia without nitrous oxide compared with the same anaesthetic with nitrous oxide (control); (iii) propofol anaesthesia without nitrous oxide (TIVA) compared with another anaesthetic with nitrous oxide (control). Efficacy (prevention of postoperative nausea and vomiting compared with control) was estimated using odds ratio and number-needed-to-treat methods, and compared within a range of 20–60% control event rates for early efficacy (0–6 h) and 40–80% for late efficacy (0–48 h). Propofol anaesthesia or omitting nitrous oxide had similar effects on vomiting, both early and late. Propofol (but not omitting nitrous oxide) decreased the incidence of nausea. TIVA studies were documented poorly; appropriate comparisons with other interventions were not possible. Efficacy of treatments should be compared within a setting-specific range of control event rates. There is insufficient evidence that TIVA with propofol is an anaesthetic technique with a low emetogenic potency. (*Br. J. Anaesth.* 1997; **78**: 256–259).

Key words

Anaesthetics i.v., propofol. Vomiting, nausea. Vomiting, antiemetics. Vomiting, incidence. Statistics. Anaesthetics gases, nitrous oxide.

Many pharmacological interventions for preventing postoperative nausea and vomiting (PONV) have been discussed over the past 30 yr.^{1–6} The relative efficacy of these interventions is documented poorly and there is no “gold standard”. This gold standard would be the most efficacious and least harmful, and increasingly, the cheapest intervention.⁷

In comparing the efficacy of different antiemetic interventions (as opposed to comparing one intervention with a control^{8,9}), a new reason for a limited range of control event rates arises. If the efficacy of intervention A has been tested mainly in studies with high control event rates, and intervention B in studies with low control event rates, then intervention A will

have more scope for improvement over its control. Therefore, the efficacy of A relative to B would be overestimated.

The choice of upper and lower limits of a restricted band of control event rates for comparing antiemetic efficacy is arbitrary. It should create a band as narrow as possible to reduce the risk of confounding comparisons of estimates of efficacy and should take into account the most likely distribution of event rates without interventions. The compromise is to achieve homogeneity of data but not to exclude too many studies. For this study, both an increased risk of PONV in populations selected for antiemetic studies (and therefore an increased likelihood for high control event rates) and an increase in the cumulative incidence of PONV over time (early *vs* late outcomes) were taken into account.

We defined an appropriate range of control event rates for PONV in which to compare the antiemetic efficacy of three different anaesthetic interventions: propofol maintenance, omitting nitrous oxide and total i.v. anaesthesia (TIVA) with propofol (that is propofol anaesthesia without nitrous oxide).

Methods

Relevant data were from three separate sources: directly from a published meta-analysis comparing propofol maintenance (intervention) with another anaesthetic (control)⁸; a reworking of a published meta-analysis of anaesthetics without nitrous oxide (intervention) compared with the same anaesthetic but with nitrous oxide (control)⁹; and a new meta-analysis of randomized, controlled studies comparing the antiemetic efficacy of TIVA with propofol (intervention) with another anaesthetic with nitrous oxide (control). Studies for this latter meta-analysis were sought using the same strategy and criteria as previously for the propofol studies (see accompanying article).⁸

For each data set of an intervention the procedure (systematic search of randomized, controlled studies, extraction of PONV data) was essentially the

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same as described previously.^{8,9} Three different PONV outcomes were extracted in dichotomous form (i.e. presence or absence of PONV): nausea, vomiting (including retching) and any emetic event (nausea or vomiting). This was done for two time periods: 0–6 h (early PONV) and 0–48 h (late PONV).

Only estimates of efficacy of studies with an early control event rate between 20 and 60% or a late control event rate between 40 and 80% were analysed and compared with each other. These PONV comparator ranges for early and late outcomes were *post hoc* definitions. The early comparator range (20–60% control event rate) was taken from another meta-analysis.⁸ The late comparator range (40–80% control event rate) was judged appropriate for the increased late control event rates found in antiemetic studies (unpublished data). Because of the difference between the two ranges, there was no intention to compare early antiemetic efficacy with late antiemetic efficacy.

Statistical significance and clinical relevance of efficacy were evaluated as described in the accompanying article.⁸ The main estimate of efficacy was the number-needed-to-treat which indicated how many patients had to be exposed to an intervention in order to prevent one particular emetic event (nausea, retching/vomiting or any emetic event) in one of them, who would have had this emetic event with the corresponding control treatment.

A statistically significant improvement of an intervention over control was assumed when the upper limit of the 95% confidence interval (CI) of the number-needed-to-treat did not include a negative value (infinity). A significant improvement of one intervention over another intervention was assumed when the 95% CI of the NNT did not overlap, although this is a notably conservative assumption.

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/propponv.html>).

Results

A comparison between TIVA with propofol and a non-propofol–nitrous oxide anaesthetic was found in nine studies^{10–18}; in only four were the control event rates within the defined ranges, either early or late.^{11,13–15} In all TIVA comparisons the control arm included induction with thiopentone and a maintenance regimen with nitrous oxide and isoflurane, enflurane or halothane.

Relevant data for the two other interventions, propofol maintenance and omitting nitrous oxide, were from a reworking of two previous meta-analyses.^{8,9}

EARLY OUTCOMES (FIG. 1)

The scatter of event rates suggested efficacy in preventing early emetic events with all interventions, especially TIVA.

When data were analysed within the early

comparator range (control event rates 20–60%) both propofol for maintenance and omitting nitrous oxide had a similar effect on early vomiting compared with the corresponding control intervention (number-needed-to-treat point estimate approximately 5). Propofol maintenance was as good at preventing early nausea or any emetic event (nausea of vomiting), whereas omitting nitrous oxide was not significantly different from control in preventing early nausea, and prevention of any emetic event was not documented within the comparator range.

Prevention of early vomiting with TIVA showed a tendency for greater efficacy than propofol maintenance or omitting nitrous oxide. However, there were insufficient relevant data with TIVA to allow meaningful comparisons with the other interventions. The analysable TIVA data set within the comparator range was based on 66 treated patients from three small studies reporting vomiting as an early outcome.^{11,13,15} The 95% confidence limits of the number-needed-to-treat to prevent early vomiting of all three interventions overlapped. Prevention of early nausea with TIVA, reported within the comparator range in only one study,¹⁴ was not different from propofol maintenance.

LATE OUTCOMES (FIG. 1)

For all three interventions there was little indication of late efficacy (to 48 h) from the event rate scatters.

Within the late comparator range (control event rates 40–80%) propofol for maintenance and omitting nitrous oxide had the same, statistically significant effect on vomiting. Propofol maintenance showed a favourable effect on late nausea (number-needed-to-treat point estimate approximately 3) but using data from only 38 patients from two small studies with contradictory results. Omitting nitrous oxide had no effect on late nausea. With both interventions prevention of any late emetic event (nausea, vomiting, or nausea and vomiting) was either not significantly different from control (omitting nitrous oxide) or not documented (propofol).

Within the late comparator range, only one TIVA study reported prevention of vomiting as an outcome¹⁵; late efficacy was not significantly different from a halogenated–nitrous oxide anaesthetic in 25 treated patients.

Discussion

Quantitative analysis of combined data extracted from systematically searched randomized controlled studies is a powerful test of the evidence that an intervention is efficacious and was used here to try to improve our poor understanding of the relative potency of antiemetic interventions.

Antiemetic efficacy may be identified in a high-risk or low-risk setting. This inequality may confound comparisons between treatments and underlines the necessity of using only studies with comparable underlying risk. Because risk is not well understood in PONV studies we have to rely on the event rate in controls who did not receive an antiemetic treatment. Indeed, we have to assume that there is a close

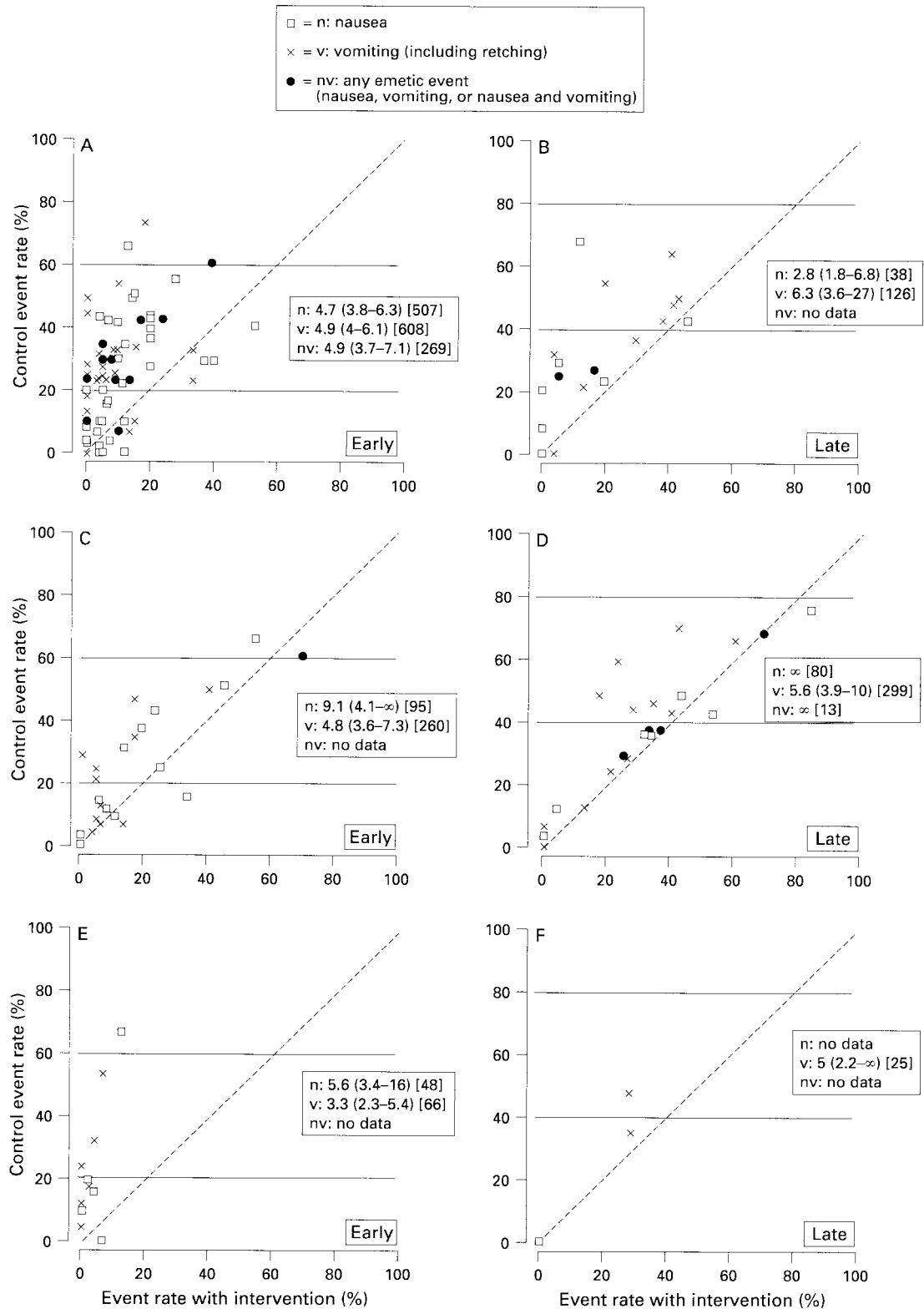


Figure 1 Early (0–6 h) and late (0–48 h) emetic event rates with: A, B: propofol maintenance (control=another anaesthetic); C, D: omitting nitrous oxide (control=same anaesthetic with nitrous oxide); E, F: total i.v. anaesthesia (control=another anaesthetic with nitrous oxide). Symbols are comparisons between an intervention and control. One study may report 1–3 different emetic events (see key), both early and late. Horizontal lines indicate early (20–60%) and late (40–80%) control event rate comparator ranges. Values are number-needed-to-treat (95% confidence interval) [numbers of treated patients] to prevent an outcome with an intervention compared with control within the comparator range. ∞ = Infinity.

relationship between underlying risk and this control event rate and, therefore, we use control event rate as an indicator of risk. We have defined a PONV comparator range of control event rates to evaluate

the effect of propofol, as an induction agent or as a maintenance regimen, on early and late PONV.⁸ In that study the logic was to eliminate those studies which had little opportunity to show an improvement

and those that were clinically irrelevant. In this study the aim was to create a narrow band of control event rates which represented outcomes of the majority of antiemetic studies. Interventions may then be compared on the same basis.

What are the clinically relevant results of this study?

A propofol maintenance anaesthetic and omitting nitrous oxide in general anaesthesia had approximately the same effect on early and late postoperative vomiting. Our model was not designed to compare early with late antiemetic efficacy as in another meta-analysis.⁸ However, these results suggest that, even in settings with an extraordinarily high risk of nausea and vomiting (i.e. 40–80% incidence of PONV without prophylaxis), approximately six patients have to be treated with either method to prevent long-term vomiting in one of them. The number-needed-to-treat confidence limits suggested that this number could be twice as high when nitrous oxide is omitted and almost five times as high when propofol is used. Such antiemetic long-term efficacy cannot be regarded as clinically relevant.

Omitting nitrous oxide had no effect on early nausea whereas propofol decreased the incidence of early nausea to the same extent as early vomiting. Prevention of late nausea with propofol maintenance suggested a favourable effect, but from only a few treated patients in two small studies with contradictory results.

Because of the very few studies in the PONV comparison range, TIVA with propofol cannot be recommended based on the present evidence. Even if subsequent studies provided enough data to show a statistically significant and clinically relevant advantage over the two other techniques, there is still the factor that nitrous oxide with propofol reduces the risk of intraoperative awareness⁹ and eventually decreases cost.^{19 20}

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