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Omission of Nitrous Oxide during Anesthesia Reduces the Incidence of Postoperative Nausea and Vomiting

A Meta-Analysis

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Background: Postoperative nausea and vomiting are important causes of morbidity after general anesthesia. Nitrous oxide has been implicated as an emetogenic agent in many studies. However, several other trials have failed to sustain this claim. The authors tried to resolve this issue through a meta-analysis of randomized controlled trials comparing the incidence of postoperative nausea and vomiting after anesthesia with or without nitrous oxide.

Methods: Of 37 published studies retrieved by a search of articles indexed in the MEDLINE database from 1966 to 1994, 24 studies (26 trials) with distinct nitrous-oxide and non-nitrous oxide groups were eligible for the meta-analysis. The pooled odds ratio and relative risk were calculated. Post hoc subgroup analysis was also performed to qualify the result.

Results: The pooled odds ratio was 0.63 (0.53 to 0.75). Omission of nitrous oxide reduced the risk for postoperative nausea and vomiting by 28% (18% to 37%). In the subgroup analysis, the maximal effect of omission of nitrous oxide was seen in female patients. In patients undergoing abdominal surgery and general surgical procedures, the effect of omission of nitrous oxide, although in the same direction, was not significant.

Conclusion: Omission of nitrous oxide reduced the odds of postoperative nausea and vomiting by 37%, a reduction in risk of 28% (Key words: Anesthetic gases: nitrous oxide. Postoperative complications: nausea and vomiting.)

POSTOPERATIVE nausea and vomiting (PONV) is an important cause of morbidity after anesthesia. Recent surveys1–5 reported incidences of nausea and vomiting ranging from 18% to 38% and 11% to 26%, respectively. Although regarded as a minor and often inevitable complication of anesthesia and surgery, PONV may cause significant distress to patients; in outpatients, it may delay discharge and necessitate hospital admission. With an increasing number of operations being performed on an ambulatory basis, such an outcome is undesirable for patients, surgeons, and anesthesiologists.6 Factors that contribute to PONV, classified broadly as patient factors, surgical factors, and anesthetic factors, have been detailed in previously published reviews.7–11 Of the anesthetic factors, nitrous oxide has received considerable attention as a potential emetogenic agent.12,13 There is evidence to suggest that use of nitrous oxide during anesthesia contributes significantly to PONV. Nitrous oxide has been shown to activate several receptor systems to produce vomiting. These include the medullary dopaminergic system,14 the sympathetic nervous system, and the opioid receptors in the brain.15 Changes in middle ear pressure,16 as well as bowel distension after diffusion of nitrous oxide into closed cavities,17 also may contribute to PONV. Nitrous oxide, when given as the sole anesthetic under hyperbaric conditions, induces vomiting in volunteers.18,19 Buffington20 used logistic regressions to reveal that patients receiving nitrous oxide during isoflurane anesthesia had a greater incidence of vomiting. If nitrous oxide does contribute to PONV, an intervention as simple as omission of nitrous oxide from the anesthetic technique could reduce postoperative morbidity, hospital admissions, costs, and distress to patients and their families. The relationship between nitrous oxide and PONV has been studied.
many times.\textsuperscript{21-52} with PONV as either the primary end point of the study or as one of several other outcomes. However, although some studies have shown a positive correlation between use of nitrous oxide and PONV, others have failed to establish any link between nitrous oxide and PONV. Thus we performed a meta-analysis of published randomized, controlled trials studying the effect of nitrous oxide on PONV to determine the impact of nitrous oxide on PONV. Meta-analysis enabled us to combine the quantitative information from several such diverse, independent studies, integrating the findings to provide a summary statistic together with its uncertainties.\textsuperscript{55}

Materials and Methods

Literature Search

An initial list of studies was obtained by searching the MEDLINE database from January 1966 to December 1994, using the terms (MESH as well as text search) \textit{anesthetic gases, nitrous oxide, postoperative complications, nausea and vomiting.} Articles were also obtained by a manual search of cross-references from original articles, review articles, correspondence, and abstracts. Only English language references were scanned. After completing the initial search, we repeated the search using appropriate key words, and no other article was identified.

Data Synthesis

Inclusion Criteria. Articles that met the following criteria were included in the meta-analysis: (1) Nitrous oxide was used for anesthesia, rather than for analgesia; (2) the study was a randomized, controlled trial; (3) nitrous oxide and non-nitrous oxide groups in the trial were distinct and had no major differences in accompanying anesthetic agents; (4) nausea, retching, or vomiting were identified as outcomes; and (5) the incidence of the outcome selected was greater than in either the nitrous oxide or non-nitrous oxide groups. Data were abstracted independently by two of the authors. There were no differences whether the data were abstracted from the two authors.

The meta-analysis was designed to determine whether omission of nitrous oxide significantly reduced the odds of PONV. The primary outcome used for the meta-analysis was vomiting, which was used in 14 trials. The other outcomes used were nausea and vomiting in 5 trials; nausea or vomiting in 1 trial; nausea in 1 trial; retching and vomiting in 2 trials; nausea, vomiting, and retching in 1 trial, and requirement for antiemetic therapy in 2 trials (table 1). However, for each individual study, the endpoint of the study was identical in the nitrous oxide and non-nitrous oxide groups. Similarly, the time of measurement of PONV was identical in the two arms of each study. Care was taken to see that the same study was not repeated as an abstract and as a full article. All patients in studies that met the criteria for inclusion were categorized into the nitrous oxide group and non-nitrous oxide group. In some studies, counts of patients with PONV in each group were available and were calculated from percentages.\textsuperscript{54,56,41,46,53}

In one study,\textsuperscript{50} the percentages of patients in each group were first derived from a graph and the absolute number of patients in each group was determined.

Muir and associates’ study\textsuperscript{39} was considered to consist of two trials (Muir-I and Muir-II) involving direct comparisons between the following nitrous oxide and non-nitrous oxide groups: (a) enflurane-N,\textsubscript{2}O,\textsubscript{2}O,\textsubscript{2} versus enflurane-air and (b) isoflurane-N,\textsubscript{2}O,\textsubscript{2}O,\textsubscript{2} versus isoflurane-air. Similarly, the study by Bloomfield and coworkers\textsuperscript{52} was treated as two trials (Bloomfield-I and Bloomfield-II): (a) sufentanil with isoflurane-N,\textsubscript{2}O,\textsubscript{2}O,\textsubscript{2} versus sufentanil with isoflurane-oxygen and (b) isoflurane-N,\textsubscript{2}O,\textsubscript{2}O,\textsubscript{2} versus isoflurane-oxygen.

In five studies,\textsuperscript{28,31,32,54,57} comprising seven trials, there were minor confounding factors. Patients in Sengupta and Plantevin’s\textsuperscript{31} study received either enflurane-N,\textsubscript{2}O,\textsubscript{2}O,\textsubscript{2} or enflurane-oxygen. In addition, significantly more patients in the non-nitrous oxide group received incremental doses of propofol during periods of light anesthesia. In one study,\textsuperscript{35} premedication was not controlled, whereas in another\textsuperscript{57} some patients received spinal or epidural anesthesia and others did not. Intraoperative fentanyl and edrophonium/atropine were given as the discretion of the anesthesiologist” in these studies.
Table 1. Summary of Studies Included for the Meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Patient, Surgery</th>
<th>Anesthetic Agents</th>
<th>Incidence of PONV/Total no. of Patients (%)</th>
<th>N2O Group</th>
<th>Non-N2O Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jastak and Goretta25</td>
<td>Adults, Oral surg.</td>
<td>Ket + N2O:O2</td>
<td>N &amp; V</td>
<td>2/18 (11%)</td>
<td>2/18 (11%)</td>
</tr>
<tr>
<td>Lonie and Harper27</td>
<td>Fem, Lap</td>
<td>F + E + N2O:O2</td>
<td>F + E + N2O</td>
<td>V, 24 h</td>
<td>20/41 (49%)</td>
</tr>
<tr>
<td>Muir et al.28</td>
<td>Adults, Gen surg.</td>
<td>(a)M + E + N2O:O2</td>
<td>(c)M + E + Air</td>
<td>V, 24 h</td>
<td>51/178 (29%)</td>
</tr>
<tr>
<td>Melnick and Johnson29</td>
<td>Fem, minor gyn.</td>
<td>I + N2O:O2</td>
<td>I + O2</td>
<td>N &amp; V, 24 h</td>
<td>8/32 (25%)</td>
</tr>
<tr>
<td>Kortila et al.30</td>
<td>Fem, Ab-Hyst</td>
<td>F + I + N2O:O2</td>
<td>F + I + O2</td>
<td>V, 24 h</td>
<td>9/55 (16%)</td>
</tr>
<tr>
<td>Gibbons et al.31</td>
<td>Ped Strabismus</td>
<td>N2O:O2 + H</td>
<td>N2 + O2 + H</td>
<td>V, 1 day</td>
<td>11/21 (52%)</td>
</tr>
<tr>
<td>Sengupta and Plantevi32</td>
<td>Fem, lap</td>
<td>F + E + N2O:O2</td>
<td>F + E + O2</td>
<td>V in hosp</td>
<td>11/33 (33%)</td>
</tr>
<tr>
<td>Bloomfield et al.33</td>
<td>Adult</td>
<td>(a)S + N2O:O2 + I</td>
<td>(c)S + O2 + I</td>
<td>V in RR</td>
<td>1/6 (30%)</td>
</tr>
<tr>
<td>Hovorka et al.34</td>
<td>Gen surg.</td>
<td>(b)N2O:O2</td>
<td>(d)O2</td>
<td>V, 24 h</td>
<td>2/16 (13%)</td>
</tr>
<tr>
<td>Lampe et al.35</td>
<td>Adult, Neuro</td>
<td>I + N2O:O2</td>
<td>I + O2</td>
<td>N or V</td>
<td>9/13 (69%)</td>
</tr>
<tr>
<td>Scheinin et al.36</td>
<td>Adult, Colon surg</td>
<td>F + I + N2O:O2</td>
<td>F + I + O2</td>
<td>N</td>
<td>5/20 (25%)</td>
</tr>
<tr>
<td>Pandit et al.37</td>
<td>Ped, T &amp; A</td>
<td>F + N2O:O2</td>
<td>F + O2</td>
<td>N &amp; V, 24 h</td>
<td>53/70 (76%)</td>
</tr>
<tr>
<td>Eger et al.38</td>
<td>Adult, Vasc. Neuro, Orth</td>
<td>I + N2O:O2</td>
<td>I + O2</td>
<td>V, 24 h</td>
<td>59/126 (48%)</td>
</tr>
<tr>
<td>Felts et al.39</td>
<td>Fem, Lap</td>
<td>E + N2O:O2</td>
<td>E + Air</td>
<td>N &amp; V in RR</td>
<td>26/69 (39%)</td>
</tr>
<tr>
<td>Watcha et al.40</td>
<td>Ped, Strabismus</td>
<td>M + Pro + N2O:O2</td>
<td>M + Pro</td>
<td>V, 24 h</td>
<td>18/30 (60%)</td>
</tr>
<tr>
<td>Ranta et al.41</td>
<td>Adult L-tomy</td>
<td>F + I + N2O:O2</td>
<td>F + I + Air</td>
<td>R &amp; V, 20 h</td>
<td>9/26 (35%)</td>
</tr>
<tr>
<td>Taylor et al.42</td>
<td>Adult Lap-chole</td>
<td>F + I + N2O:O2</td>
<td>F + I + Air</td>
<td>AET in RR</td>
<td>9/26 (35%)</td>
</tr>
<tr>
<td>Wilson and Fell43</td>
<td>Ped M-tomy</td>
<td>N2O:O2 + H</td>
<td>O2 + H</td>
<td>V, 24 h</td>
<td>10/47 (21%)</td>
</tr>
<tr>
<td>Jensen et al.44</td>
<td>Adults, Lap-chole</td>
<td>F + I + N2O:O2</td>
<td>F + I + Air</td>
<td>AET</td>
<td>10/18 (50%)</td>
</tr>
<tr>
<td>Pedersen et al.45</td>
<td>Fem, Ab-hyst</td>
<td>F + I + N2O:O2</td>
<td>F + I + Air</td>
<td>V, 24 h</td>
<td>12/17 (71%)</td>
</tr>
<tr>
<td>Reimer et al.46</td>
<td>Ped, Strabismus</td>
<td>Pro + N2O:O2</td>
<td>Pro + O2</td>
<td>V, 24 h</td>
<td>11/24 (42%)</td>
</tr>
<tr>
<td>Sukhani et al.47</td>
<td>Fem, lap</td>
<td>Pro + N2O:O2</td>
<td>Pro + Air</td>
<td>N, R &amp; V, 24 h</td>
<td>10/34 (29%)</td>
</tr>
<tr>
<td>Pandit et al.48</td>
<td>Ped, T &amp; A</td>
<td>F + H + N2O:O2</td>
<td>F + H + O2</td>
<td>R &amp; V, 24 h</td>
<td>20/30 (67%)</td>
</tr>
<tr>
<td>Splinter et al.49</td>
<td>Ped M-tomy</td>
<td>H + N2O:O2</td>
<td>H + O2</td>
<td>V, 24 – 48 h</td>
<td>21/158 (13%)</td>
</tr>
</tbody>
</table>

Fem = females; I = laparoscopy; surg = surgery; gyn = gynecological surgery; Gen = general; Ab-hyst = abdominal hysterectomy; Ped = pediatric; neuro = neurosurgery; T & A = tonsilllectomy and/or adenoidectomy; Vasc = vascular surgery; Orth = orthopedic surgery; L-tomy = laparotomy; Lap-chole = laparoscopic cholecystectomy; M-tomy = myringotomy; Ket = ketamine; F = fentanyl; N2 = nitrogen; E = enflurane; I = isoflurane; M = morphine; S = sufentanil; pro = propofol; H = halothane; N = nausae; V = vomiting; hosp = hospital; RR = recovery room; R = retching; AET = requirement for antiemetic therapy.

* Studies with moderate confounding factors.

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The types of surgical procedures in three studies28,52-57 were varied, and patients were not stratified according to surgical procedure. The meta-analysis was repeated after excluding these studies.

**Studies Excluded from the Meta-analysis.** None of the review articles or correspondence were eligible for inclusion. Thirty-seven original articles and abstracts were evaluated for inclusion in the meta-analysis. Seven of the 37 articles were excluded from the meta-analysis for the following reasons: (a) in two studies, nitrous oxide was used for analgesia21,24; (b) three studies were not randomized trials21,24; (c) in two studies, it was not possible to determine the number of patients in the nitrous oxide and non-nitrous oxide groups22,52; and (d) the study by Gunawardene and White53 was excluded because the incidence of vomiting was zero in both the non-nitrous oxide and nitrous oxide groups. The exclusion of this small study (n = 58, which is 2.1% of the total number of patients in the meta-analysis) is not expected to affect the final result significantly. Six randomized studies33,42-44,58 were excluded from the analysis. In these studies, the nitrous oxide and non-
nitrous oxide groups were not strictly comparable, because additional anesthetic agents were used. The differences in these additional anesthetic agents could have affected the incidence of PONV.

Statistical Methods

The difference between the observed (O) and expected (E) incidence in PONV (O-E) and the variance was calculated for each study using standard methods. A negative value for the difference indicated that the incidence of PONV was lower in the non-nitrous oxide group. The odds ratios of each trial, defined as the ratio of the odds of PONV in the non-nitrous oxide group to the odds of PONV in the nitrous oxide group, was calculated by dividing the difference between O and E by the variance of that trial. The individual variances and the value of O - E and the event rates (occurrence of PONV) were combined to obtain the pooled odds ratio (POR) with confidence intervals (CI). To measure effect size, a fixed effect model was used. The relative risk, defined as the ratio of the proportion of patients experiencing PONV in the non-nitrous oxide group to the proportion of patients with PONV in the nitrous oxide group, was derived from the POR. The risk reduction, which is the proportional reduction in risk for PONV in the non-nitrous oxide group, compared with the risk in the nitrous oxide group, was calculated as follows: Percentage risk reduction = (1 - relative risk) × 100. Here we used the terms risk reduction and reduction in risk interchangeably.

The results were expressed graphically, indicating the OR and CI of each study and the POR and CI of the overview. Inclusion of an odds ratio of 1 in the CI indicated that the result was not significant. The studies were tested for heterogeneity using the chi-squared test.

Subgroup Analysis

Meta-analyses were performed on the following subgroups. (1a) Studies confined to adult women; (1b) pediatric patients; (2a) isoflurane or enfurane anesthetics; (2b) intravenous anesthesia, with nitrous oxide being used in the nitrous oxide group and no other anesthetic gas or vapor used in the non-nitrous oxide group; (3a) studies performed exclusively in patients having laparoscopic surgery; (3b) studies in patients having intraabdominal surgery; and (3c) studies performed in adult patients having dental, general surgical, neurosurgical, and miscellaneous procedures not included in 3a and 3b.

Table 1 summarizes 26 trials from 24 studies included in the meta-analysis. Figure 1 shows that in 20 of the 26 trials, the odds of PONV in the non-nitrous oxide group was lower than those in the nitrous oxide group. However, the result was statistically significant in only five trials. In four trials, an equal proportion of patients experienced PONV in both groups. In two trials, omission of nitrous oxide produced an effect in the opposite direction. In the overview, the POR was 0.63 (95% CI, 0.53 to 0.75; P < 0.0001), a reduction of the odds of PONV of 37% in the non-nitrous oxide group. The test of heterogeneity was negative (χ² = 35.8; degrees of freedom = 25; P = 0.1), implying that the magnitude of this effect was reliable. This corresponds to a relative risk for PONV of 0.72 (CI 0.63 – 0.82) in the non-nitrous oxide group, and a risk reduction by 28% (18% to 37%). If the seven trials with minor confounding factors are excluded, the POR is 0.55 (95% CI, 0.44 to 0.70) and the test of heterogeneity is negative.

Subgroup Analysis

Table 2 lists the results of the meta-analyses of the various subgroups. The maximal beneficial effect of omission of nitrous oxide was seen in female patients. The POR in patients having abdominal surgery and miscellaneous surgical procedures was not statistically significant. In the subgroup of patients undergoing laparoscopic surgery, the POR was significant, but the test of heterogeneity was positive. If the only study that showed an effect of omission of nitrous oxide in the opposite direction is excluded, there is no heterogeneity in the subgroup, the POR is 0.45 (CI, 0.31 to 0.61) and is statistically significant, translating to a risk reduction of 43% (24% to 58%).

Discussion

This meta-analysis shows that omission of nitrous oxide results in a risk reduction of PONV by 28% (18% to 37%).

The results of the various randomized, controlled trials of nitrous oxide and PONV conflict. There were only five statistically significant “positive” trials, showing that omission of nitrous oxide decreased PONV. There were 15 “negative” trials, two trials in which elimination of nitrous oxide increased PONV (not statistically significant), and no effect in four trials. Thus, vote...
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Fig. 1. Meta-analysis of randomized trials comparing incidence of PONV with or without omission of nitrous oxide. The odds ratios (OR) are plotted on the X axis on a logarithmic scale. The position of each solid square represents the OR of each trial. The horizontal line indicates the 95% confidence interval. In each trial, squares to the left of unity (OR = 1) imply that omission of nitrous oxide reduced PONV; squares to the right of unity imply that omission of nitrous oxide increased PONV.

A well-designed, randomized, controlled, double-blind trial with adequate power to detect an effect remains the gold standard method to prove or disprove a hypothesis. However, most trials in this meta-analysis were undersized. In the absence of one or more ideal trials, combining the results of several studies through the techniques of meta-analysis produces a more precise estimate of the effect and hence provides stronger evidence for or against a non-nitrous oxide effect.53 The validity of the meta-analysis depends on the quality of the literature search. Our search strategy has yielded articles not included in previously published reviews.

Table 2. Results of the Meta-analyses of Subgroups

<table>
<thead>
<tr>
<th>Group</th>
<th>Reference Nos.</th>
<th>Incidence of PONV (%)</th>
<th>POR</th>
<th>TH</th>
<th>Risk Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>25, 27–32, 34–41, 45–51, **, ††</td>
<td>821/2756</td>
<td>34</td>
<td>26</td>
<td>0.63 - ve</td>
</tr>
<tr>
<td>Females</td>
<td>27, 29, 30, 31, 34, 38, 47, 49</td>
<td>195/712</td>
<td>35</td>
<td>20</td>
<td>0.43 - ve</td>
</tr>
<tr>
<td>Children</td>
<td>**, ††, 39, 45, 48, 50, 51</td>
<td>250/760</td>
<td>38</td>
<td>28</td>
<td>0.57 - ve</td>
</tr>
<tr>
<td>I/E anesthetics</td>
<td>27–29, 30, 32, 34–36, 37, 38, 40, 41, 46, 47</td>
<td>533/1826</td>
<td>35</td>
<td>25</td>
<td>0.65 - ve</td>
</tr>
<tr>
<td>IV anesthetics</td>
<td>25, 39, 48, 49</td>
<td>66/215</td>
<td>39</td>
<td>23</td>
<td>0.46 - ve</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>30, 36, 40, 47</td>
<td>59/236</td>
<td>30</td>
<td>20</td>
<td>0.56 + ve</td>
</tr>
<tr>
<td>Laparoscopic surgery</td>
<td>27, 31, 34, 38, 41, 46, 49</td>
<td>192/596</td>
<td>39</td>
<td>26</td>
<td>0.53 + ve</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>25, 28, 32, 35, 37</td>
<td>311/1104</td>
<td>31</td>
<td>26</td>
<td>0.78 - ve</td>
</tr>
</tbody>
</table>

POR = pooled odds ratio; TH = test of heterogeneity; I/E = isoflurane or enflurane; IV = intravenous.

Risk reduction (%) = (1 - RR) x 100, where RR = relative risk.

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on the subject. Because we have restricted our search to published articles (including abstracts), data from unpublished work is not included. The quality of meta-analysis may also be affected by publication bias. Small, positive trials are more likely to be published than negative ones, distorting the findings of the meta-analysis.30

However, in our meta-analysis, the number of "negative" trials exceeds the number of positive trials confirming the emetic effect of nitrous oxide. Publication bias, if it does exist, appears to be in a direction opposing the conclusions of the meta-analysis. Most (16 of 26) of the trials included in the meta-analysis accrued fewer than 100 patients each. Thus the meta-analysis is open to criticism that it is based largely on small trials.30 However, the effect of the overview is in the same direction as that of the largest studies.29,37

The robustness of our meta-analysis can be gauged from an estimate of the size and results of a study that, if added to the existing studies in the meta-analysis, would refute the conclusion of the overview (that omission of nitrous oxide significantly reduces the odds of PONV). In a study of 800 patients, with a 30% incidence of PONV in the nitrous oxide group consisting of 400 patients, 185 patients (46.5%) in the non-nitrous oxide group would have to suffer from PONV so that the CI in the overview would include 1 and thus render the difference between the nitrous oxide and non-nitrous oxide groups insignificant. No such study exists in the current meta-analysis. On the other hand, exclusion of the largest study,29 consisting of 718 patients, increases the magnitude of the effect but does not change the conclusion of the meta-analysis.

A common objection raised against meta-analyses is that, given the differences between the various trials, "apples are being compared to pears and oranges." It is important to understand that patients from one trial are not directly compared with patients from another trial; instead, the difference between O and E and the variance of all trials are pooled to obtain the POR. Thus, although there may be differences between trials with respect to types of patients, surgical procedures and drugs used during anesthesia, and the endpoint or outcome studied, these variations among trials are not important provided all such factors are matched in the non-nitrous oxide and nitrous oxide groups in each trial.34

It is tempting to conclude that nitrous oxide should be avoided in all patients, because doing so would reduce the risk for PONV by 28%. A recent, non-meta-analytic review37 showed that in 24 of 27 studies, a greater incidence of emesis is associated with nitrous oxide, and the two-tailed probability that this has occurred by chance is less than 0.00005. However, to determine whether omission of nitrous oxide may be more useful in certain types of patients, procedures, or anesthetics than in others, we have cautiously ventured into the treacherous area of subgroup analysis, which suggested that the omission of nitrous oxide may reduce the risk for PONV to the greatest extent in female patients. This may be related to hormonal changes during the menstrual cycle that may affect susceptibility to PONV.8,30,35 The subgroup analysis also suggested that the risk for PONV in patients undergoing abdominal or miscellaneous procedures may not be reduced after omission of nitrous oxide. However, none of the trials have directly compared male and female patients or abdominal surgery with other types of operations. Thus we emphasize that the results of our subgroup analysis should be interpreted with caution and should only guide hypothesis generation and design of further randomized trials.

In a recently published meta-analysis, Tramer and colleagues80 used the number-needed-to-treat (NNT; i.e., the number of patients who must be treated for one patient to benefit from the intervention) as a measure of effect size. The NNT is easy to interpret in clinical terms, and it accounts for the risk reduction as well as the basal incidence rate in the control group.81 Tramer and colleagues80 found that omission of nitrous oxide significantly reduced the risk for early (6 h) and late vomiting (48 h) after anesthesia, with a combined NNT of 13 (CI, 9 to 30), but had no effect on the incidence of nausea or on complete emetic control. Their meta-analysis also included studies of desflurane as an anesthetic that are not included in our analysis. In addition, they defined post hoc subgroups as those having a baseline risk lower or higher than that of the mean of all trials. They found no significant reduction in the risk for early or late vomiting in patients with a lower baseline risk, but in patients with a high baseline risk, omission of nitrous oxide-oxide significantly reduced the risk for both early and late vomiting, with NNTs of 5 and 6, respectively. However, creation of subgroups based on endpoint studied (early and late vomiting), further subdivided into low and high baseline risks for vomiting, may have reduced the event rate in the control group, leading to an increase in the NNT. This can mathematically reduce the significance of a potentially beneficial treatment effect. In addition, this approach cannot prospectively identify groups at high risk for outcomes associated with the use of any anesthetic.82

The factors that might be related to the risk for PONV are summarized in the Table. The risk for PONV is significantly increased in patients with non-nitrous oxide anesthesia; only 7% of studies included in our analysis were performed in patients who received non-nitrous oxide anesthesia.

Omission of nitrous oxide in controlled, prospective clinical trials is not supported (1) to reduce the risk for PONV (such an intervention generating gene)

References


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risk for PONV. Nevertheless, their results broadly agree with those of our meta-analysis. The NNT to reduce any PONV in our study is approximately 10.

The finding that omission of nitrous oxide reduces the risk for PONV by as much as 28% needs to be applied in clinical practice. This must be balanced by the resultant increase in the risk for patient awareness. Tramer and colleagues' meta-analysis found a significant increase in the risk for patient awareness in the non-nitrous oxide group, but the NNT was large (46.2), only 7 of the 24 trials studied commented on patient awareness, and the number of patients included was small.

Omission of nitrous oxide can reduce the risk for PONV by nearly 30%. Further studies and randomized, controlled trials are needed (1) to elucidate the etiologic mechanism of nitrous oxide, (2) to determine prospectively the subgroups who would have the greatest clinical benefit from omission of nitrous oxide, and (3) to determine the incidence of adverse outcomes (such as awareness) after omission of nitrous oxide during general anesthesia.

References


42. Raftery S, Sherry E: Total intravenous anaesthesia with propofol and alfentanil protects against postoperative nausea and vomiting. Can J Anaesth 1992; 39:37–40


