ANESTHESIOLOGY

Perioperative Supplemental Oxygen and Postoperative Nausea and Vomiting: Subanalysis of a Trial, Systematic Review, and Meta-analysis

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ANESTHESIOLOGY 2023; 138:56–70

What We Already Know about This Topic

- Postoperative nausea and vomiting are uncomfortable for patients and occasionally cause morbidity.
- The theory that intraoperative supplemental oxygen might reduce postoperative nausea and vomiting dates to the 1990s, but the evidence is mixed.

What This Article Tells Us That Is New

- The investigators conducted a subanalysis of a previous trial that evaluated the effect of 80% *versus* 30% intraoperative inspired oxygen on surgical site infection after colorectal surgery. Supplemental oxygen did not reduce the incidence of postoperative nausea and/or vomiting, the number of rescue antiemetic doses given, time to administration of the first rescue antiemetic, or severity of postoperative nausea or vomiting. In a meta-analysis that includes the current results and all relevant previous trials, supplemental oxygen did not reduce postoperative nausea or vomiting, overall or separately, for abdominal or nonabdominal surgery.

ABSTRACT

Background: Intraoperative supplemental oxygen may reduce postoperative nausea and vomiting by mitigating hypoxic stress on the gastrointestinal tract. The authors therefore tested the hypothesis that supplemental oxygen reduces nausea and vomiting in adults recovering from colorectal surgery at the Cleveland Clinic between January 28, 2013, and March 11, 2016.

Methods: Initially, the authors conducted an unplanned subanalysis of a previous trial that evaluated the effect of 80% *versus* 30% intraoperative inspired oxygen on surgical site infection. Specifically, they assessed the effect of 80% *versus* 30% oxygen concentration on the incidence of postoperative nausea and/or vomiting. Thereafter, the authors conducted a systematic review and meta-analysis of the effect of supplemental oxygen on postoperative nausea and vomiting.

Results: The authors' underlying analysis included 5,057 colorectal surgeries on 4,001 patients. For 2,554 surgeries, assignment was to 80% oxygen, and in 2,503 surgeries, to 30%. Postoperative nausea and vomiting was 852 of 2,554 (33%) in 80% oxygen and 814 of 2,503 (33%) in 30% oxygen. The estimated relative risk (95% CI) of 80% *versus* 30% oxygen on postoperative nausea and vomiting was 1.04 (0.96 to 1.12) in a generalized estimating equation model adjusting for within-patient correlation for patients with multiple surgeries, $P = 0.355$. Furthermore, supplemental oxygen did not reduce antiemetic use ($P = 0.911$) or the severity of nausea and vomiting ($P = 0.924$). The authors' meta-analysis included 10 qualifying trials (6,749 patients) and did not find a difference in postoperative nausea and vomiting: relative risk, 0.97 [95% CI, 0.86 to 1.08], $P = 0.55$, $I^2 = 52\%$.

Conclusions: The incidence of postoperative nausea and vomiting did not differ in patients assigned to 80% or 30% inspired oxygen. A meta-analysis of available trials similarly indicated that supplemental intraoperative oxygen does not reduce postoperative nausea and vomiting. Therefore, supplemental oxygen should not be given in the expectation that it will reduce nausea and vomiting.

(ANESTHESIOLOGY 2023; 138:56–70)

Postoperative nausea and vomiting causes patient dissatisfaction and occasionally causes morbidity.[1] Even with prophylactic antiemetic treatment, about one-third of surgical patients experience postoperative nausea, vomiting, or both.[2–4]

The theory that intraoperative supplemental oxygen might reduce postoperative nausea and vomiting gained momentum in the 1990s, based on the hypothesis that inadequate oxygen

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Submitted for publication February 10, 2022. Accepted for publication October 21, 2022. Published online first on November 1, 2022.

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 Anesthesiology 2023; 138:56–70. DOI: 10.1097/ALN.0000000000004428

supply to gastrointestinal tissues triggers release of serotonin from local vagal afferent nerve terminals.[5–7] Serotonin, once released, might then activate emetic brain centers, as demonstrated in nonoperative circumstances.[8]

Greif *et al.*[6] were the first to explore the use of perioperative supplemental oxygen (80% oxygen *vs.* 30% oxygen) to reduce postoperative nausea and vomiting in a cohort of patients having colorectal resections, concluding that supplemental oxygen reduces postoperative nausea and vomiting. However, subsequent trials of supplemental oxygen for mitigation of postoperative nausea and vomiting reported divergent results.[9–17] We therefore tested the primary hypothesis that supplemental intraoperative oxygen (80%) reduces the incidence of postoperative nausea and vomiting compared with 30% inspired oxygen in adults who had major abdominal surgery. Furthermore, we conducted a systematic review and meta-analysis of the effect of supplemental oxygen on postoperative nausea and vomiting.

Materials and Methods

The underlying trial was approved by the Cleveland Clinic Institutional Review Board (Cleveland, Ohio; CC-IRB 12-891) and registered on https://www.clinicaltrials.gov (trial number: NCT01777568, registration date: January 29, 2013, principal investigator: Andrea Kurz, M.D.). The systematic review was registered on the PROSPERO registry with the number CRD42020212494.

Trial Methodology

We conducted a *post hoc* subanalysis of a cluster-crossover trial by Kurz *et al.*[18] published in 2018. The trial tested the hypothesis that supplemental oxygen reduces surgical site infections in patients having colorectal surgery—which it did not. In brief, an isolated suite of operating rooms at the Cleveland Clinic Department of Colorectal Surgery alternated between 80% and 30% intraoperative supplemental oxygen at 2-week intervals for 39 months. Per protocol, the oxygen concentration was increased as necessary to maintain oxygen saturation 95% or greater. A total of 5,749 adults who had intestinal surgery lasting at least 2 h were enrolled between January 28, 2013, and March 11, 2016. For our subanalysis, added inclusion criteria were that the patients remained hospitalized for at least 24 h and had postoperative nausea or vomiting records (fig. 1).

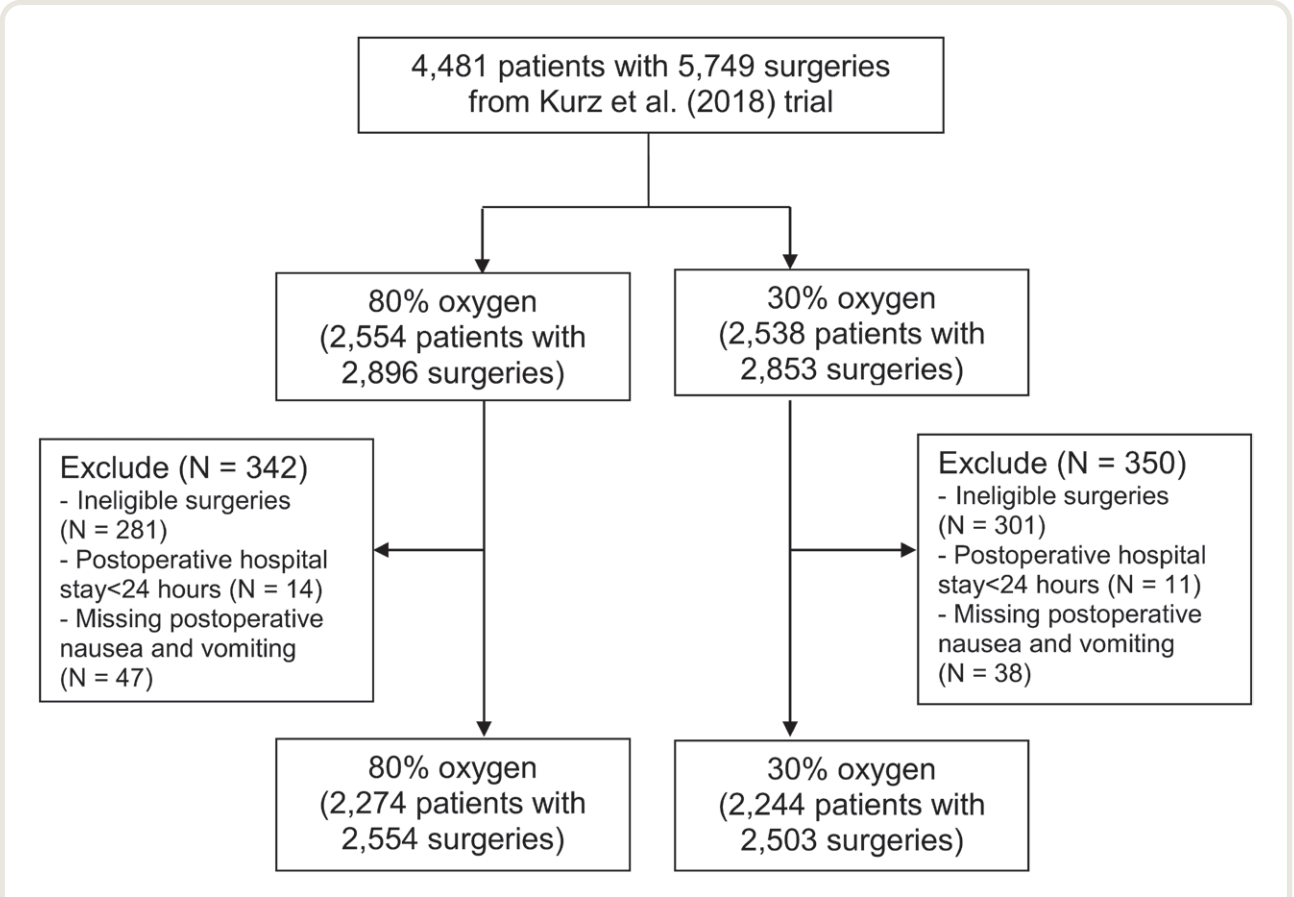


Fig. 1. Consolidated Standards of Reporting Trials diagram.

Patient-reported postoperative nausea and vomiting severity was collected by nurses in the postanesthesia care unit every 15 min for 2 h on a scale of 0 ("none to minimal"), 1 ("moderate"), and 2 ("severe"). Thereafter, nurses evaluated postoperative nausea and vomiting at 4-h intervals throughout hospitalization. Additionally, time to administration of the first rescue antiemetic was determined from electronic medical records.

We further reported intraoperative antiemetics and postoperative opioid use.[19] Most patients were given 4 mg ondansetron and 8 mg dexamethasone intraoperatively. In recovery and on the wards, patients experiencing nausea and/or vomiting were given 4 mg ondansetron, 25 mg promethazine, a scopolamine patch 1.5 mg per 72 h, or 10 mg prochlorperazine.

Data Analysis for Trial

Patients assigned to 80% and 30% oxygen were compared on demographic, baseline, and procedural variables using standard descriptive statistics and the absolute standardized difference (*i.e.,* the absolute difference in means or proportions divided by the pooled standard deviation). We defined an imbalance between groups as an absolute standardized difference greater than 0.10. Additional baseline variables reported included the Apfel postoperative nausea and vomiting risk score (based on current smoking), individual components of the risk score, and preoperative antiemetics. We planned to adjust for baseline variables with an absolute standardized difference greater than 0.10 in all statistical models (in fact all absolute standardized differences were less than 0.10, so no adjustment was needed).

The primary outcome variable was at least one episode of postoperative nausea and/or vomiting, evaluated dichotomously, as documented in nursing notes over the initial 24 h after surgery. Secondary outcomes included the number of rescue antiemetic treatments over 24 h, time to administration of initial rescue antiemetic (if given), and patient-reported severity of nausea documented in the postanesthesia care unit within the first 2 h after surgery. We chose to measure the number of antiemetic doses, because the efficacy of various antiemetics has been shown to be comparable.[20]

Categorical variables were described using frequencies and percents, and continuous variables described using either medians and quartiles or means ± SDs. All analyses adjust for potential within-subject correlation across multiple surgeries.

We assessed the treatment effect of 80% *versus* 30% oxygen concentration on the primary outcome of any postoperative nausea and vomiting using a generalized estimating equation model with log link (to estimate relative risk) and adjusting for within-patient correlation across multiple surgeries assuming an exchangeable correlation structure. For the number of rescue antiemetic doses, we assessed the treatment effect using a generalized estimating equation model with identity link adjusting for within-patient correlation across multiple surgeries assuming an exchangeable correlation and estimating the difference in means. As a sensitivity analysis we used a Wilcoxon rank-sum test with Hodges-Lehmann estimator of median difference. For the 3-level severity of nausea outcome, we assessed the treatment effect using a proportional odds generalized estimating equation model with cumulative logit link and an independence within-patient correlation structure. Results would be interpreted as the odds of being in a worse category of the outcome for 80% *versus* 30% oxygen. As a sensitivity analysis we used the Mantel–Haenszel chi-square for ordered outcomes. For time to administration of initial rescue antiemetic, we assessed the treatment effect using a Cox proportional hazards frailty model, with patient considered as a random "frailty" effect. All effect estimates were accompanied by 95% CIs.

The incidence of postoperative nausea and vomiting reported in the literature ranges from 30% in the general surgical population to 80% in high-risk cohorts.[4,19] After reviewing previous reports and input from practicing anesthesiologists, we *a priori* designated that a 20% relative reduction or larger in the proportion with nausea and vomiting would be clinically meaningful. Conservatively assuming a proportion of only 20% with the outcome in the 30% oxygen group (control), 3,874 surgeries would be needed to detect a relative risk of 0.80 or stronger at the 0.05 significance level in a two-tailed test of proportions. With our 5,057 surgeries, we had 96% power to detect a relative risk of 0.80 or stronger.

The significance level for all hypotheses was 0.05. Statistical analyses were performed using R Software (https://www.R-project.org/) and SAS 9.4 software (SAS Institute, USA). Meta-analyses were performed using Review Manager (RevMan [computer program], version 5.4, The Cochrane Collaboration, 2020, United Kingdom).

Systematic Review and Meta-analysis

Our systematic review includes 15 trials with a total of 7,723 surgeries and serves as an update of the review published by Hovaguimian *et al.* in 2013.[21] We followed the Cochrane Handbook for Systematic Reviews of Interventions and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[22,23] Meta-analysis was conducted on the primary outcome of postoperative nausea and vomiting.

A medical librarian executed a multilevel search strategy outlined in appendix 1 in the Supplemental Digital Content (http://links.lww.com/ALN/C954). First, we searched the following databases: PubMed, Ovid EMBASE, Google Scholar, ClinicalTrials.gov, and Cochrane Central Register of Controlled Trials, from August 20, 2020, to September 29, 2020. Then, we checked the bibliographies of primary studies and review articles for additional references.

Trial Selection

We included trials in adults who had general anesthesia where the assigned low inspired oxygen (FIO_2) was less than

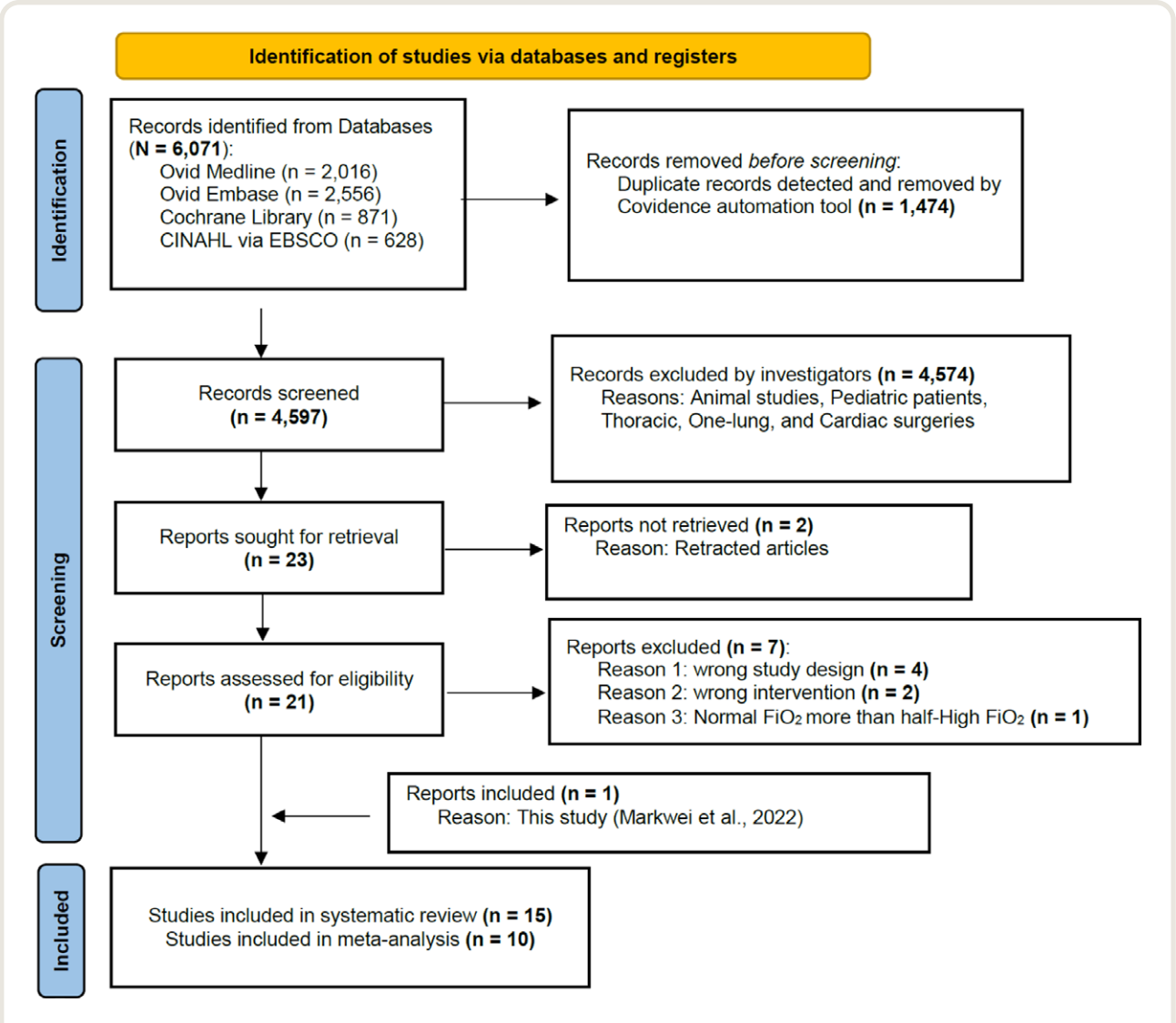


Fig. 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram for new systematic reviews that included searches of databases and registers only. FIO_2, fraction of inspired oxygen.

half the assigned high FIO_2. We excluded non-English publications,[24] retracted articles, articles without available full-text, and articles reporting one-lung, thoracic, or cardiac surgeries.

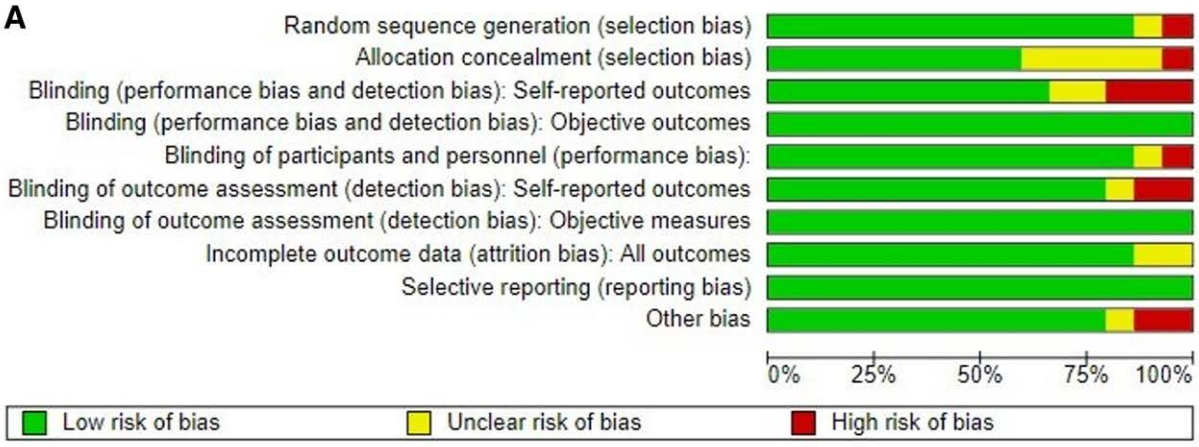
Three investigators (M.M., H.E., E.K.) independently screened titles and abstracts of studies, retrieved full-text reports of trials, and recorded reasons why ineligible studies were excluded. Disagreements were resolved by consensus or by consulting a senior member of the team (D.I.S.). We excluded duplicates and recorded the selection process in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (fig. 2).

Data Extraction

We used a database collection form in Covidence, a web-based platform that streamlines systematic review production. Investigators (M.M., I.B., E.K., H.E.) independently extracted the following characteristics and outcome data from the included studies: trial design, location, population, sample size, intervention, and comparison groups. One investigator entered data into the Review Manager 5 file (version 5.4.1; The Nordic Cochrane Centre, The Cochrane Collaboration, Denmark), and another spot-checked trial characteristics for accuracy.

Assessment of Risk of Bias

Three investigators (M.M., E.K., H.E.) independently assessed the risk of bias for each trial using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions:



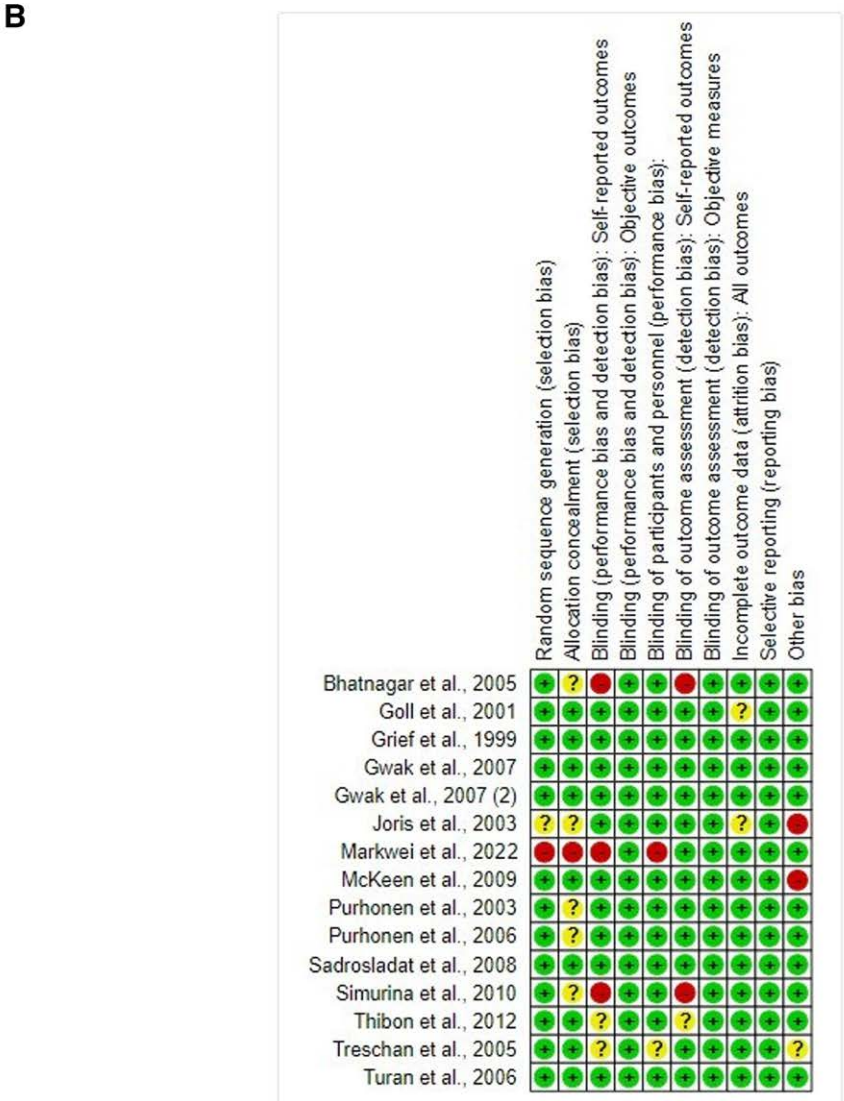


Fig. 3. Cochrane Risk of Bias Assessment for Randomized Control Trials.

- Allocation (selection bias)
- Blinding (performance bias and detection bias)
- Incomplete outcome data (attrition bias)
- Selective outcome reporting (reporting bias)
- Other bias

We graded each potential source of bias as high, low, or unclear—and provided a quote from the trial report as justification. Finally, a risk-of-bias graph and summary table were constructed using Review Manager (fig. 3).

Data Synthesis

We recorded each trial's design, as well as its population, intervention, comparisons, and outcomes. We then assessed the quality of evidence for the primary outcome of postoperative nausea and vomiting across studies using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) for the following domains: risk of bias, precision, consistency, directness, and publication bias (appendix 4a, http://links.lww.com/ALN/C954).[25,26] Trial outcomes were entered into the data and analyses tables in Review Manager 5.

Treatment effects were evaluated using meta-analysis and expressed using pooled relative risks for any nausea and/or vomiting using the Mantel–Haenszel method to aggregate the relative risks, accompanied by the corresponding 95% CI. A random-effects model (DerSimonian and Laird) was used to account for potential clinical and statistical heterogeneity. We calculated Cochran's Q statistic and its chi-square test for heterogeneity (*i.e.*, heterogeneity beyond that expected by sampling variability, measurement error, or chance), and we also quantified heterogeneity with the I^2 statistic. Treatment effect estimates for individual studies and across studies in the meta-analysis were displayed using forest plots.

We assessed potential publication bias (or nonreporting bias) for the treatment effect on postoperative nausea and vomiting by visualizing the funnel plots of observed treatment effect by standard error of treatment effect, and using Egger's test for asymmetry in the funnel plot.[27] In an attempt to explain some of the observed heterogeneity, we planned to assess whether the effect of 80% *versus* 30% oxygen on postoperative nausea and/or vomiting varied by sex or by surgery type (*i.e.*, whether there was evidence of a treatment-by-covariate interaction). However, although some female-only studies were found, no male-only studies were found. Therefore, we only studied whether surgery type would explain some of the heterogeneity (appendix 3a and 3b, http://links.lww.com/ALN/C954). The GRADEpro Guideline Development Tool Software was used to summarize results (appendix 4b, http://links.lww.com/ALN/C954).[28]

Results

Trial

Our subanalysis included 4,001 patients who had 5,057 colorectal surgeries at the Cleveland Clinic Main Campus from January 28, 2013, to March 11, 2016. A total of 2,274 patients with 2,554 surgeries were assigned to 80% intraoperative oxygen and 2,244 patients with 2,503 surgeries were assigned to 30% oxygen. Summary statistics are presented in table 1 as percentage of patients, means ± SDs, or medians [quartiles]. As previously reported, baseline characteristics were similar in patients assigned to 80% and 30% intraoperative oxygen (all absolute standardized differences less than 0.10, table 1).[18] The mean ± SD intraoperative average oxygen concentration was 78 ± 12% in patients assigned to 80% oxygen and 42 ± 10% in those assigned to 30% oxygen. There were no clinically meaningful differences between the 80% and 30% oxygen groups on the proportion of patients receiving preoperative antiemetics (3% *vs.* 2%, absolute standardized difference = 0.019) or intraoperative antiemetics (97% *vs.* 98%, absolute standardized difference = 0.072).

The incidence of postoperative nausea and vomiting did not differ in surgeries assigned to 80% and 30% oxygen: 852 of 2,554 (33%) in cases assigned to 80% O_2 *versus* 814 of 2,503 (33%) in surgeries assigned to 30% O_2: relative risk, 1.04 [95% CI, 0.96 to 1.12], $P = 0.355$ (table 2). The median [quartiles] number of antiemetic doses given within the first 24 h was 0 [0, 1] for 80% oxygen and 0 [0, 1] for 30% oxygen. The mean difference (95% CI) in number of antiemetic doses between groups was 0.003 (–0.04 to 0.05), $P = 0.911$ (table 2). Supplemental oxygen (80%) had no significant effect on the number of rescue antiemetic doses given during the initial 24 postoperative hours (table 2).

Postoperative nausea and vomiting severity during the initial two postoperative hours did not differ between the oxygen groups, with proportional odds ratio (95% CI) of 1.01 (0.85 to 1.19), $P = 0.924$ (table 2), and most patients in both groups reporting "none to minimal" nausea. Time to administration of antiemetics did not differ either, with an estimated hazard ratio of 1.03 [0.93, 1.13], $P = 0.567$ (fig. 4).

Systematic Review and Meta-analysis

In our systematic review, 6,071 references were identified and imported for screening; 1,474 duplicates were removed, leaving 4,597 studies to be screened against the title and Abstract. Of these, 4,574 studies were excluded, and 23 studies were assessed for full-text eligibility. Nine full-text articles were excluded for the following reasons: English full-text unavailable (3), article retracted (2), full text not available (2), normal F_{IO_2} was more than half the high F_{IO_2}

Table 1. Demographic, Baseline, and Surgical Characteristics by the Percentage of Inspired Oxygen Given (N = 5,057 surgeries)

	80% O_2 2,554 Surgeries (2,274 Patients)	30% O_2 2,503 Surgeries (2,244 Patients)	Absolute Standardized Difference
Age, yr	52 ± 17	52 ± 17	0.004
Body mass index, kg/m²	27 ± 6	27 ± 7	0.025
Race, n (%)			0.043
Caucasian	2,323 (91)	2,249 (90)	
African American	177 (7)	202 (8)	
Others	54 (2)	52 (2)	
Apfel risk factors, n (%)			
Sex			
Male	1,231 (48)	1,178 (47)	0.023
Female	1,323 (52)	1,325 (53)	
Smoking status			0.069
Current smoker	284 (11)	228 (9)	
Ex-smoker	716 (28)	737 (29)	
Never smoker	1,554 (61)	1,538 (61)	
History of postoperative nausea and vomiting	433 (17)	445 (18)	0.022
History of motion sickness	576 (23)	589 (24)	0.023
Had preoperative antiemetic	69 (3)	60 (2)	0.019
Had intraoperative antiemetic	2,465 (97)	2,446 (98)	0.072
Had postoperative opioid	2,434 (95)	2,392 (96)	0.013
Apfel risk score, n (%)			0.091
0	2 (0.1)	5 (0.2)	
1	194 (8)	142 (6)	
2	1,038 (41)	1,033 (41)	
3	947 (37)	919 (37)	
4	373 (15)	404 (16)	
American Society of Anesthesiologists physical status, n (%)			0.018
I	10 (1)	10 (1)	
II	816 (32)	807 (32)	
III	1,564 (61)	1,516 (61)	
IV	163 (6)	169 (6)	
V	1 (0)	1 (0)	
Past medical history/comorbidities, n (%)			
Diabetes	230 (9)	210 (8)	0.022
Cancer	656 (26)	600(24)	0.040
Obesity	499 (20)	537 (22)	0.047
Psychoses	129 (5)	125 (5)	0.003
Depression	510 (20)	474 (19)	0.026
Alcohol and substance abuse	100 (4)	101 (4)	0.006
Primary preoperative diagnosis, n (%)			0.024
Cancer	577 (24)	560 (24)	
Crohn's disease	409 (17)	405 (17)	
Ulcerative colitis	472 (20)	470 (20)	
Ostomy surgery	228 (9)	207 (9)	
Others	727 (30)	706 (30)	
Surgical and anesthetic details			
Had preoperative bowel-preparation medication	455 (18)	442 (18)	0.004
Minimal alveolar concentration of anesthetic gas (h)	3 ± 2	3 ± 2	0.005
Crystalloid volume, l	2,903 ± 1,360	2,947 ± 1,405	0.032
Colloid volume, l	211 ± 399	235 ± 414	0.058
Had regional block	68 (3)	105 (4)	0.084
Had spinal or epidural anesthesia	272 (11)	246 (10)	0.027
Duration of surgery, min	255 ± 109	258 ± 112	0.036
Laparoscopic surgery (*vs.* open or converted)	635 (25)	633 (25)	0.010
Surgery type, n (%)			0.030
Colorectal resection	1,245 (49)	1,225 (49)	
Ostomy	65 (3)	65 (3)	
Excision, lysis peritoneal adhesions	57 (2)	51 (2)	
Hernia repair	46 (2)	49 (2)	
Other lower gastrointestinal therapeutic procedures	861 (34)	828 (33)	
Laparoscopy, exploratory laparotomy	106 (3)	114 (4)	
Small-bowel resection	174 (7)	171 (7)	

Data reported as n (%) or mean ± SD. No data were missing for any variables in table 1.

Table 2. Primary and Secondary Outcome Results

	80% O_2 (2,274 Patients, 2,554 Surgeries)	30% O_2 (2,244 Patients, 2,503 Surgeries)	Estimate (95% CI)	*P* Value
Postoperative nausea and vomiting at 24 h	852 (33)	814 (33)	1.04 (0.96 to 1.12)*	0.355*
Number of rescue antiemetic doses at 24 h			0.003 (–0.04 to 0.05)†	0.911†
0	1,438 (56)	1,386 (55)		
1	749 (29)	768 (31)		
2	284 (11)	270 (11)		
3	62 (2)	62 (2)		
4	18 (0.7)	16 (0.6)		
5	2	1		
6	1	0		
Postoperative nausea and vomiting severity at 2 h			1.01 (0.85 to 1.19)‡	0.924‡
None to minimal	2,237 (88)	2,191 (88)		
Moderate	253 (10)	242 (9)		
Severe	64 (2)	70 (3)		

Treatment effect of 80% *versus* 30% oxygen was assessed for the primary outcome of any postoperative nausea and vomiting in the first 24 h and for secondary outcomes of the number of postoperative antiemetics and severity of postoperative nausea and vomiting in the first 24 h. No data were missing for any variables in table 2. Values are expressed as numbers of patients (%).

*Relative risk (95% CI) and *P* value from a log-binomial generalized estimating equation model adjusting for within-patient correlation across multiple surgeries, assuming an exchangeable correlation structure.

†Difference in means (95% CI) and *P* value from a generalized estimating equation model with identity link adjusting for within-patient correlation across multiple surgeries, assuming an exchangeable correlation. Sensitivity analysis: Wilcoxon rank-sum test $P = 0.676$.

‡Proportional odds ratio (95% CI) and *P* value from a generalized estimating equation model with cumulative logit link and independence within-patient correlation structure. Sensitivity analysis: Mantel–Haenszel chi-square test for ordered outcomes $P = 0.775$.

group (1), and one study used propofol in addition to 80% oxygen (1). The selection procedure is summarized in figure 2, and the trial characteristics are shown in table 3.

Our meta-analysis included 10 trials including the results of this current subanalysis, representing 6,749 patients. All of the studies randomly assigned individual patients, except ours, which used a cluster crossover design. Meta-analyses of all included trials showed little evidence of a benefit of perioperative administration of high (80%) F_{IO_2} on the prevention of postoperative nausea and vomiting compared with the 30% F_{IO_2} group: relative risk, 0.97 [0.86, 1.08], $P = 0.55$, $I^2 = 52\%$ (fig. 5). Of note, the overall risk ratio of the meta-analyses weighted more toward the three larger studies: Markwei *et al.* (2022, the current analysis), McKeen *et al.* (2009),[16] and Turan *et al.* (2006).[14] Appendix 2 (http://links.lww.com/ALN/C954) shows evidence of asymmetry in the funnel plot, suggesting at least some publication bias for the treatment effect on postoperative nausea and vomiting. The *P* value for Egger's test for the postoperative nausea and vomiting outcome was not significant ($P = 0.08$), although the test was not well powered.

Finally, we conducted interaction tests to assess whether some of the observed treatment effect heterogeneity could be explained by surgery type (abdominal *vs.* nonabdominal). There was not convincing evidence that surgery type influenced the effect of intraoperative supplemental oxygen (80% *vs.* 30%) on the incidence of postoperative nausea and vomiting, with interaction test $P = 0.17$. The relative risk was 0.87 [0.72, 1.05] for abdominal and 1.06 [0.87, 1.28] for nonabdominal surgeries (appendix 3a, http://links.lww.com/ALN/C954). Results were similar when analysis was restricted to female patients (appendix 3b, http://links.lww.com/ALN/C954).

Certainty of Evidence

We judged the body of evidence regarding the cumulative incidence of postoperative nausea and vomiting at 24 h after surgery to be of low certainty. We downgraded the certainty of evidence due to concerns with inconsistency and imprecision (appendix 4a, http://links.lww.com/ALN/C954). I^2 of 52% revealed considerable heterogeneity, which contributed to the inconsistency.

Discussion

Trial

Supplemental oxygen did not reduce postoperative nausea and vomiting, nausea and vomiting severity, or the need for rescue antiemetics. Our results are consistent with recent trials of supplemental oxygen that also reported no significant reductions in postoperative nausea and vomiting.[10–12,14–16,29] However, they contrast with the two initial trials of supplemental oxygen and postoperative nausea and vomiting by Greif *et al.*[6] (1999; n = 231) and Goll *et al.*[9] (2001; n

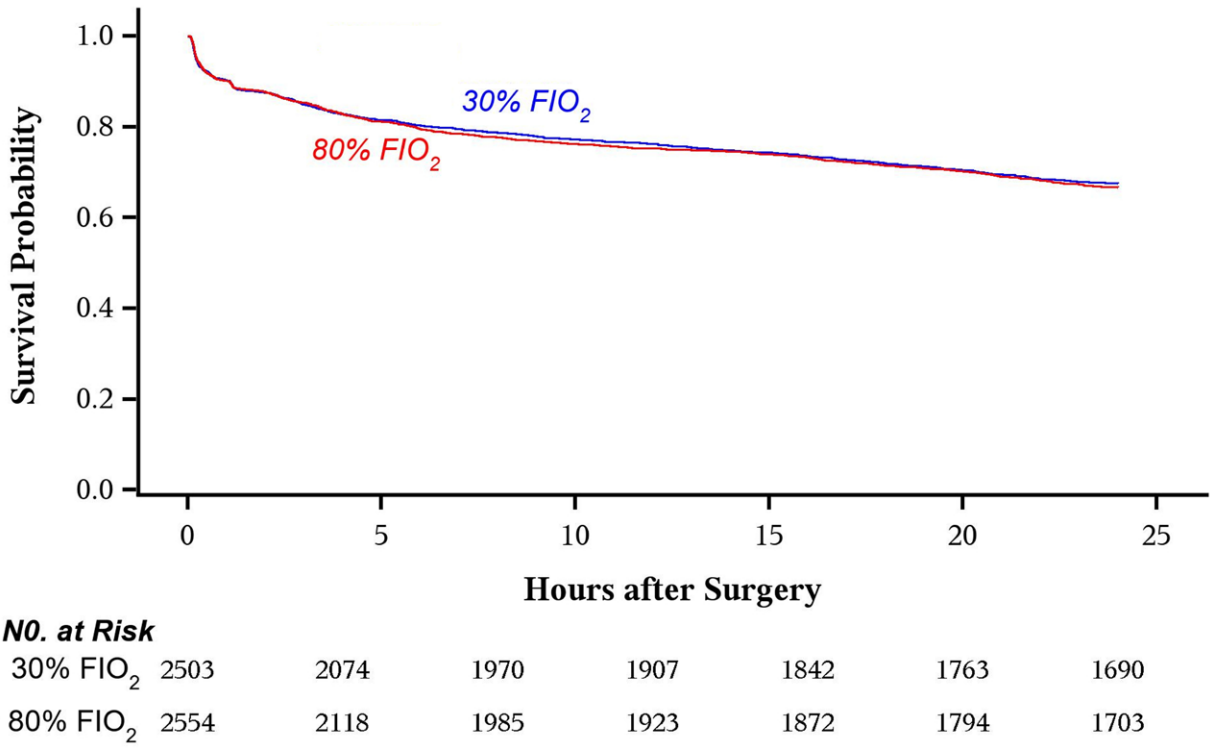


Fig. 4. Time to administration of first rescue antiemetic for 80% *versus* 30% oxygen groups. Estimated hazard ratio for association between 80% *versus* 30% inspired oxygen and postoperative nausea and vomiting was 1.03 (95% CI, 0.93 to 1.13), $P = 0.567$. F_{IO_2}, fraction of inspired oxygen.

= 159), both of which showed that 80% oxygen halved postoperative nausea and vomiting. It remains unclear why these technically adequate trials reported results that have not subsequently been replicated. However, we note that both were conducted two decades ago and that anesthetic practice has changed much in the intervening years. Both trials were also relatively small by current standards, so that chance may have been a factor. By way of contrast, our current trial included 10 times as many patients as both combined.

The *post hoc* nature of our subanalysis precluded the inclusion of potentially important variables that were not collected in the parent trial, such as the number of episodes of vomiting. For example, we could not determine which participants used selective serotonin antagonists (selective serotonin uptake inhibitors), which might matter because serotonin is strongly emetogenic. However, baseline conditions such as depression (approximately 20%) and psychoses (approximately 5%) were balanced between the 80% and 30% oxygen groups and might be used as a proxy for selective serotonin uptake inhibitors and other serotonin antagonists. Furthermore, serotonin antagonists are no more effective than other antiemetics in reducing the incidence of postoperative nausea and vomiting. Nearly all patients were given intraoperative antiemetics, usually ondansetron and dexamethasone, which presumably reduced the observed incidence of postoperative nausea and vomiting. However, use was comparable in each group and does not explain the lack of benefit from supplemental oxygen.

A limitation of our trial is that we did not randomly assign individual patients, instead using a cluster-crossover design during 39 months. Nevertheless, the trial was effectively randomized, as evidenced by highly similar baseline variables for patients assigned to 80% and 30% oxygen. An additional limitation is that, although patients were blinded to oxygen allocation, trial personnel were not. However, floor nurses who collected patient-reported severity of nausea and vomiting would not usually know how much oxygen was used intraoperatively.

Meta-analysis

The potential benefit of perioperative supplemental oxygen in reducing postoperative nausea and vomiting has been contentious. In 2008, two meta-analyses addressed the topic with disparate results. One concluded that supplemental oxygen reduced the incidence of postoperative vomiting only, and the other was unable to identify any beneficial effect of supplemental oxygen.[30,31] The most recent meta-analyses by Hovaguimian *et al.*[21] in 2013 also showed

Table 3. Characteristics of Articles Included in the Systematic Review and Meta-analysis

Author	Year	Country	Study Design	Population	Sample size (N)	High FIO_2	Low FIO_2	Outcome	Outcome Measurement	Results	Notes
Greif *et al.*[6]	1999	USA	Randomized control trial	Adults having colon or rectum resection	231	80%	30%	Postoperative nausea and vomiting	Nausea was rated on a three-point scale as none, mild, or severe. Vomiting was rated as none, mild, moderate, or severe. Outcome was measured over intervals from 0 through 6 h and 6 through 24 h	Incidence of postoperative nausea and vomiting during 24 h: 80% O_2 = 30% 30% O_2 = 17% *P* = 0.027	Supplemental oxygen resulted in the statistically significant reduction of postoperative nausea and vomiting. Nearly 2-fold decrease observed after colorectal surgery
Goll *et al.*[9]	2001	Austria	Randomized control trial	Adults having gynecologic laparoscopy	159	80%	30%	Postoperative nausea and vomiting	Nausea rated on a 4-point scale as none, mild, moderate, or severe was measured during 24-h period from 0 to 6 h and from 6 to 24 h	Incidence of postoperative nausea and vomiting during 24 h: 80% O_2 = 22% 30% O_2 = 44% Ondansetron = 30% *P* = 0.003	Supplemental oxygen resulted in statistically significant reduction of postoperative nausea and vomiting
Joris *et al.*[34]	2003	Belgium	Randomized control trial	Adults having thyroidectomy	150	80%	30%	Postoperative nausea and vomiting	Nausea was measured on 4-point scale as none, mild, moderate, or severe Outcome was measured during periods of 0–2 h, 2–6 h, 6–24 h	Incidence of postoperative nausea and vomiting during 24 h: 80% O_2 = 46% 30% O_2 = 48% Droperidol = 22%	Supplemental oxygen did not result in statistically significant reduction of postoperative nausea and vomiting
Purhonen *et al.*[10]	2003	Finland	Randomized control trial	Adults having ambulatory gynecologic laparoscopy	100	80%	30%	Postoperative nausea and vomiting	Incidence of nausea, vomiting, or both during the initial 24 h after surgery	Incidence of postoperative nausea and vomiting during 24 h: 80% O_2 = 55% 30% O_2 = 62% *P* = 0.486	Supplemental oxygen did not result in statistically significant reduction of postoperative nausea and vomiting Symptoms of postoperative nausea and vomiting occurred earlier after 80% oxygen than after 30% oxygen
Bhatnagar *et al.*[11]	2005	USA	Randomized control trial	Adult women having modified radical mastectomy	40	80%	30%, 50%	Postoperative nausea and vomiting	Postoperative nausea and vomiting was measured on a numeric rank scale postoperative nausea and vomiting score: 0 = no nausea/vomiting 1 = nausea alone 2 = vomiting once 3 = vomiting 2 or more times in 30-min interval. Postoperative nausea and vomiting was evaluated within the first 24 h after anesthesia at intervals of 0–2, 2–6, 6–24 h	Incidence of postoperative nausea and vomiting during 24 h: 80% O_2 = 30% 50% O_2 = 45% 30% O_2 = 35% *P* = 0.906	No significant difference between the groups

(*Continued*)

Table 3. (Continued)

Author	Year	Country	Study Design	Population	Sample size (N)	High FIO_2	Low FIO_2	Outcome	Outcome Measurement	Results	Notes
Treschan *et al.*[12]	2005	USA	Randomized control trial	Adults having strabismus surgery	139	80%	30%	Postoperative nausea and vomiting	Vomiting was categorized as none, 1, 2 or 3, or more than 3 episodes Severities of nausea and postoperative pain were each rated on a 4-point scale as none, mild, moderate, or severe Postoperative nausea and vomiting was evaluated 6 and 24 h postoperatively	Incidence of postoperative nausea and vomiting during 24 h: 80% O_2 = 38% 30% O_2 = 41% 30% O_2 + ondansetron = 28% P = 0.279	No statistically significant difference of postoperative nausea and vomiting incidence among groups.
Purhonen *et al.*[29]	2006	Finland	Randomized control trial	Adult women having breast surgery	90	80%	30%	Postoperative nausea and vomiting	Nausea was scored using a linear scale from 0 to 10 (0 = no nausea, 10 = nausea "as bad as it can be"). Postoperative nausea and vomiting was evaluated during 24 postoperative hours at 1, 2, 6, and 24 h after surgery	Incidence of postoperative nausea and vomiting during 24 h: 80% O_2 = 17% 30% O_2 = 11% P = 0.027	No statistically significant difference between the groups
Turan *et al.*[14]	2006	USA	Randomized control trial	Adults having elective surgeries with general anesthesia	559	80%	30%	Postoperative nausea and vomiting	Postoperative nausea and vomiting was classified as: Early (first 2 h) or late (2–24 h) based on time after anesthesia	Incidence of postoperative nausea and vomiting during 24 h: 80% O_2 = 31% 30% O_2 = 24% P = 0.061 Postoperative nausea and vomiting in abdominal surgery: 80% O_2 = 40% 30% O_2 = 31% P = 0.37 Postoperative nausea and vomiting in nonabdominal surgery: 80% O_2 = 25% 30% O_2 = 21% P = 0.368	Supplemental oxygen was unable to reduce postoperative nausea and vomiting regardless of end point, observational period, or site of surgery.
Gwak *et al.*[36]	2007	Korea		Adult women having thyroidectomy	100	80%	30%	Postoperative nausea and vomiting	Postoperative nausea and pain were evaluated with 10 cm visual analog scale (0 = none; 10 = severe). Postoperative nausea and vomiting was measured by interviewing patients before operation and 2, 6, and 24 h postoperatively	Incidence of postoperative nausea and vomiting during 24 h: 80% O_2 = 90% 30% O_2 = 90%	No differences in the incidence and the severity of postoperative nausea and vomiting were observed postoperatively between the groups

(*Continued*)

Table 3. (Continued)

Author	Year	Country	Study Design	Population	Sample size (N)	High FIO_2	Low FIO_2	Outcome	Outcome Measurement	Results	Notes
Gwak *et al.* (2)[15]	2007	Korea		Adults having laparotomy and laparoscopic abdominal or gynecologic surgery	200	80%	30%	Postoperative nausea and vomiting	Patients were asked to rate the severity of postoperative nausea and pain with 10 cm visual analog scale: 0 = none; 1–3 = mild; 4–6 = moderate; 7–10 = severe Postoperative nausea and vomiting was evaluated 2, 6 and 24 h postoperatively	Incidence of postoperative nausea and vomiting during 24 h: 30% O_2 + 6 ml·kg^{-1}·h^{-1} Hartman's solution infusion = 38% 30% O_2 + 18 ml·kg^{-1}·h^{-1} Hartman's solution infusion = 50% 80% O_2 + 6 ml·kg^{-1}·h^{-1} Hartman's solution infusion = 48% 80% O_2 + 18 ml·kg^{-1}·h^{-1} Hartman's solution infusion = 44%	There were no statistically significant differences among the 4 groups in the incidence of postoperative nausea and vomiting patients
Sadrolsadat *et al.*[35]	2008	Iran	Randomized control trial	Adults having inguinal hernia surgery	100	70%	30%	Postoperative nausea and vomiting	Nausea and vomiting were evaluated from 0 to 6 h and from 6 to 24 h postoperatively.	Incidence of postoperative nausea and vomiting during 24 h: 70% O_2 = 14% 30% O_2 = 40% $P < 0.0001$	Significant difference observed between the groups
McKeen *et al.*[16]	2009	Canada	Randomized control trial	Adult women having gynecologic laparoscopy	292	80%	30%	Postoperative nausea and vomiting	Nausea was assessed as: none, mild, moderate, or severe; Vomiting was any emetic episode or retching	Incidence of postoperative nausea and vomiting during 24 h: 80% O_2 = 69% 30% O_2 = 65% $P = 0.62$	No differences observed in nausea alone, vomiting
Šimurina *et al.*[17]	2010	Croatia	Randomized control trial	Adult women having gynecologic laparoscopic surgery	72	80%	30%, 50%		Frequency of nausea, vomiting, and both was assessed for early postoperative nausea and vomiting (0–2 h) and late postoperative nausea and vomiting (2–24 h)	Incidence of postoperative nausea and vomiting during 24 h: 80% O_2 = 33% 50% O_2 = 25% 30% O_2 = 36% $P = 0.572$	High intraoperative FIO_2 of 0.8 and FIO_2 of 0.5 did not prevent postoperative nausea and vomiting in patients without antiemetic prophylaxis. An intraoperative FIO_2 of 80% has a beneficial effect on early vomiting only
Thibon *et al.*[33]	2012	France	Randomized control trial	Adult patients having abdominal, gynecologic, and breast surgery	434	80%	30%	Postoperative nausea and vomiting	Incidence of nausea and vomiting was measured as an adverse event and secondary outcome variable in the study	Incidence of nausea and vomiting was: 80% O_2 = 7.5% 30% O_2 = 5.3% $P = 0.34$	Incidence of nausea and vomiting was similar between the two groups
Markwei *et al.*	2022	USA	*Post hoc* analyses	Adults having colorectal surgery	5057	80%	30%	Postoperative nausea and vomiting	Postoperative nausea and vomiting was classified as: None, minimal, moderate, severe during 24 h	Incidence of postoperative nausea and vomiting during 24 h: 80% O_2 = 34% 30% O_2 = 33% $P = 0.526$	No significant difference observed between the groups

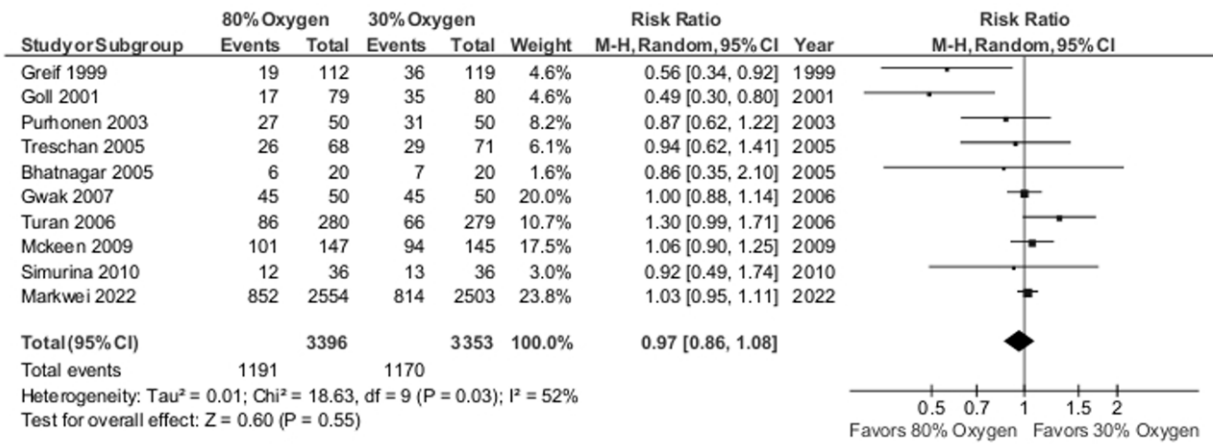


Figure 5. Forest plot analysis comparing the incidence of postoperative nausea and vomiting in participants who received 80% O_2 compared with those who received 30% O_2. M-H, Mantel–Haenszel test.

that supplemental oxygen reduces the risk of postoperative nausea and vomiting to some extent, although mainly in patients given volatile anesthesia without prophylactic antiemetics. Furthermore, two international consensus panels in 2007 and 2020 did not recommend supplemental oxygen to prevent postoperative nausea or vomiting.[4,32] Our meta-analysis, enhanced by the 5,057 surgeries in the Kurz *et al.*[18] substudy, similarly shows that supplemental oxygen does not reduce nausea or vomiting, or the need for antiemetics after colorectal surgery.

Abdominal surgery physically disturbs the intestines, provoking release of serotonin, which is powerfully emetic. It is therefore plausible that supplemental oxygen would be especially effective for abdominal surgery. We therefore conducted a treatment-by-covariate analysis within our meta-analysis to assess whether the treatment effect of supplemental oxygen on postoperative nausea and vomiting depended on the type of surgery (abdominal or nonabdominal). Intraoperative supplemental oxygen did not affect postoperative nausea and vomiting differently for abdominal and nonabdominal surgery (nonsignificant interaction test), and no benefit of supplemental oxygenation was observed for either type of surgery.

Conclusions

In our trial, there was no statistically significant or clinically meaningful difference in postoperative nausea and vomiting incidence, number of rescue antiemetic doses, time to administration of the first rescue antiemetic, or severity of postoperative nausea or vomiting in patients assigned to 80% and 30% oxygen. Our meta-analysis similarly concludes that supplemental oxygen does not reduce postoperative nausea or vomiting, overall or separately for abdominal or nonabdominal surgery. Supplemental oxygen should therefore not be given in the expectation that it will reduce nausea and vomiting.

Acknowledgments

The authors acknowledge Loren Hackett, M.L.I.S., A.H.I.P. (Cleveland Clinic Floyd D. Loop Alumni Library, Cleveland, Ohio) for her thorough database search for their systematic review.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: ds@ccf.org. Raw data available collaboratively at: ds@ccf.org.

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Supplemental Digital Content

Appendices, http://links.lww.com/ALN/C954

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