ANESTHESIOLOGY

Postoperative Pulmonary Complications in the ENIGMA II Trial: A *Post Hoc* Analysis

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ABSTRACT

Background: Nitrous oxide promotes absorption atelectasis in poorly ventilated lung segments at high inspired concentrations. The Evaluation of Nitrous oxide In the Gas Mixture for Anesthesia (ENIGMA) trial found a higher incidence of postoperative pulmonary complications and wound sepsis with nitrous oxide anesthesia in major surgery compared to a fraction of inspired oxygen of 0.8 without nitrous oxide. The larger ENIGMA II trial randomized patients to nitrous oxide or air at a fraction of inspired oxygen of 0.3 but found no effect on wound infection or sepsis. However, postoperative pulmonary complications were not measured. In the current study, *post hoc* data were collected to determine whether atelectasis and pneumonia incidences were higher with nitrous oxide in patients who were recruited to the Australian cohort of ENIGMA II.

Methods: Digital health records of patients who participated in the trial at 10 Australian hospitals were examined blinded to trial treatment allocation. The primary endpoint was the incidence of atelectasis, defined as lung atelectasis or collapse reported on chest radiology. Pneumonia, as a secondary endpoint, required a diagnostic chest radiology report with fever, leukocytosis, or positive sputum culture. Comparison of the nitrous oxide and nitrous oxide–free groups was done according to intention to treat using chi-square tests.

Results: Data from 2,328 randomized patients were included in the final data set. The two treatment groups were similar in surgical type and duration, risk factors, and perioperative management recorded for ENIGMA II. There was a 19.3% lower incidence of atelectasis with nitrous oxide (171 of 1,169 [14.6%] *vs.* 210 of 1,159 [18.1%]; odds ratio, 0.77; 95% CI, 0.62 to 0.97; $P = 0.023$). There was no difference in pneumonia incidence (60 of 1,169 [5.1%] *vs.* 52 of 1159 [4.5%]; odds ratio, 1.15; 95% CI, 0.77 to 1.72; $P = 0.467$) or combined pulmonary complications (odds ratio, 0.84; 95% CI, 0.69 to 1.03; $P = 0.093$).

Conclusions: In contrast to the earlier ENIGMA trial, nitrous oxide anesthesia in the ENIGMA II trial was associated with a lower incidence of lung atelectasis, but not pneumonia, after major surgery.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- High intraoperative inspired nitrous oxide concentrations have been associated with adsorption atelectasis, but the impact on postoperative pulmonary complications remains controversial
- The original ENIGMA trial reported more postoperative pulmonary complications and wound infections with inspired 70% nitrous oxide/30% oxygen compared to 20% nitrogen/80% oxygen
- The ENIGMA II trial studied a greater proportion of patients undergoing major vascular and fewer abdominal surgeries, comparing either inspired nitrous oxide or nitrogen with 30% oxygen, focused on cardiovascular and septic complications
- ENIGMA II did not evaluate postoperative pulmonary complications

What This Article Tells Us That Is New

- This study reanalyzed the ENIGMA II data from 10 Australian centers (approximately 33% of the total multinational cohort) to compare the incidence of atelectasis in the two treatment groups
- In contrast to the original ENIGMA trial, there was a lower incidence of atelectasis with use of nitrous oxide
- There was no effect of nitrous oxide on the secondary outcomes of pneumonia, combined pulmonary complications, or hospital length of stay

This article has been selected for the Anesthesiology CME Program (www.asahq.org/JCME2023APR). Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue. This article is featured in "This Month in Anesthesiology," page A1. This article is accompanied by an editorial on p. 345. This article has a related Infographic on p. A17. This article has an audio podcast. Part of the work presented in this article has been presented at the Australian and New Zealand College of Anaesthetists Clinical Trials Network Strategic Research Workshop in Brisbane, Queensland, Australia, August 6, 2022.

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Postoperative pulmonary complications are a common and serious source of morbidity in patients undergoing major surgery, with substantial associated healthcare costs.[1–3] The effectiveness of various perioperative strategies, such as tidal volume and positive end-expiratory pressure (PEEP) settings, to reduce the risk of pulmonary complications remains unclear.[4,5] However, avoidance of nitrous oxide was shown in the multicenter Evaluation of Nitrous oxide In the Gas Mixture for Anesthesia (ENIGMA) trial to reduce the incidences of postoperative atelectasis, pneumonia, and sepsis.[6] ENIGMA was a large (n = 2,050) pragmatic multicenter randomized trial in patients undergoing major surgery. Patients received either 70% nitrous oxide with 30% oxygen or 20% nitrogen with 80% oxygen. The incidence of clinically significant postoperative pulmonary complications was measured by chest radiography and postoperative blood and microbiology testing, which was ordered by the treating surgical team where clinically indicated in line with routine postoperative management.

The ENIGMA trial was followed by the larger ENIGMA II trial (n = 7,011), which compared the incidence of perioperative cardiovascular and septic complications, in high-risk patients undergoing major surgery. Patients in ENIGMA II received either 70% nitrous oxide or 70% nitrogen, both with 30% oxygen.[7] In contrast to ENIGMA, no difference in measured major postoperative outcomes between treatment arms was found in ENIGMA II. However, the trial did not prospectively collect data on postoperative pulmonary complications, and it therefore remains unclear whether a contribution of nitrous oxide to postoperative pulmonary complications in ENIGMA II should be expected or not.

It was considered feasible to effectively replicate the methodology of ENIGMA in measurement of pulmonary outcomes with *post hoc* collection of similar data from patients recruited to ENIGMA II. We determined whether nitrous oxide inclusion in general anesthesia was associated with a higher incidence of atelectasis and pneumonia in the cohort of patients who had been recruited to the ENIGMA II trial within Australia. This consisted of greater than 2,600 patients or approximately 35% of total trial recruitment, with comparable expected statistical power to the original ENIGMA trial in examining the effect of nitrous oxide on the incidence of postoperative pulmonary complications.

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Materials and Methods

ENIGMA II Trial Protocol

The ENIGMA II trial was a large, multicenter, international randomized trial (ClinicalTrials.gov identifier NCT00430989) funded by the Australian National Health and Medical Research Council (grant No. GNT436677) and led by the Australian and New Zealand College of Anaesthetists Clinical Trials Network between 2007 and 2013.[8] Eligible patients were adults aged at least 45 yr who were at risk of cardiovascular complications and who were having noncardiac surgery under general anesthesia that was expected to last more than 2 h. Cardiac risk factors included a history of coronary artery disease, heart failure, cerebrovascular disease, or peripheral vascular disease or older age (70 yr old or older) with other comorbidities. With written informed consent, patients were randomized to receive general anesthesia including a gas mixture containing a fraction of inspired oxygen (F_{IO_2}) of 0.3 in either nitrogen or nitrous oxide. Patients in whom a higher intraoperative F_{IO_2} was planned, including those having thoracic surgery requiring one-lung ventilation, and patients with substantially impaired lung gas exchange were excluded. A high compliance rate with treatment allocation was achieved in the trial, with only 0.5% of those patients randomized to the nitrous oxide group failing to receive the allocated gas mixture.[7]

Intraoperative patient management in the ENIGMA II trial was as follows.[7] After induction of anesthesia and airway instrumentation, anesthesia maintenance was commenced with the randomized gas mixture supplemented by volatile anesthetic agent and/or intravenous propofol and was continued until completion of surgery. Arterial haemoglobin oxygen desaturation was managed at the attending anesthesiologist's discretion with any appropriate airway or ventilatory maneuver, including increased F_{IO_2} if necessary. All patients otherwise received standard anesthetic and other perioperative care. Ventilator settings, including tidal rate and volume, PEEP, and ventilatory mode (volume or pressure control ventilation), were not prescribed. Anesthetic depth was adjusted according to clinical judgment with or without assistance from processed electroencephalograph monitoring. Neuraxial or other regional anesthetic techniques could be used to supplement general anesthesia. Anesthesiologists were expected to give prophylactic antibiotics according to local routine practice and were advised to avoid intraoperative hypothermia using available patient warming devices.

Post Hoc Pulmonary Outcome Data Collection

Ethics approval for the ENIGMA II trial had been obtained at each participating site, including all participating Australian hospitals.[7] Ethics approval for the current *post hoc* study at these hospitals was obtained from the Human Research Ethics Committee at Austin Health, Victoria (November 7, 2018, HREC/46023/Austin-2018) with subsequent approvals by site research offices in line with Australian National Mutual Acceptance provisions.

Recruitment data from the ENIGMA II trial database revealed that 15 Australian hospital sites participated in the trial, with a total of 2,642 patients included in the final data set. Five hospitals who had recruited a combined total of only 38 patients were excluded from the current study for reasons of economy, leaving a target total sample size of 2,604 patients across 10 sites. Given the *post hoc* nature of the current study, retrospective registration of the current study was lodged with the Australian and New Zealand Clinical Trials Registry (ACTRN12622000279729), after the expected sample size was determined and before unblinding of group allocation and statistical analysis.

This *post hoc* study sought to measure the incidence of postoperative pulmonary complications (defined as either pulmonary atelectasis or pneumonia or both) that occurred in the first 30 postoperative days after the index surgery after randomization. The definitions of atelectasis and pneumonia were identical to those used in ENIGMA.[6] The presence of pulmonary atelectasis required confirmation of lung atelectasis or collapse by chest x-ray or computed tomography report. Pneumonia was defined as the presence of a radiologic infiltrate confirmed by chest x-ray or computed tomography report, in association with at least one of the following: temperature greater than 38°C, leukocyte count greater than 12,000/ml, or positive sputum culture that was not heavily contaminated with oral flora or that corresponded with positive blood cultures. Due to its rarity in this population, pneumothorax was not examined as an endpoint in the current study. As was the case with the earlier ENIGMA trial and because of the primary focus of ENIGMA II on perioperative cardiovascular outcomes, comprehensive data on ventilatory settings such as tidal rate and volume, PEEP, and ventilatory mode (for example volume or pressure control) were not recorded in ENIGMA II and were not available for collection in this *post hoc* study.

Data linkage was done manually by a study coinvestigator at each participating hospital where temporary patient reidentification for all recruited trial patients was performed. This used archived ENIGMA II trial recruitment logs, blinded to trial treatment allocation, which were retrieved at each hospital to identify recruited patients and to allow interrogation of hospital digital medical records for the required data for the index hospital admission. Digitized hospital radiology records from the 30 postoperative days after the index surgery were examined first, to determine which patients had radiological confirmation required for both atelectasis and pneumonia endpoints, with subsequent interrogation of hospital pathology and microbiology records where positive radiological findings were present. Collated data at each center were subsequently deidentified before combination of data from all hospitals on a central database. All endpoint data for the current *post hoc* study were reviewed by two investigators, and a consensus decision was arrived at when it was unclear whether the data available for a given patient met the criteria for one or the other endpoint. All data remained blinded to treatment allocation, and the randomization code was not unblinded until the database had been finalized. The study methodology was piloted with data from two hospitals (Alfred and Austin hospitals, Melbourne) before additional data collection from the remaining centers nationally.

Statistical Analysis

The primary comparison was the incidence of pulmonary atelectasis between the two treatment groups. The incidence of atelectasis in the ENIGMA trial was 7.5% in the control group and 13% in the nitrous oxide group (odds ratio [95% CI], 0.57 [0.42 to 0.77]).[6] In the current *post hoc* study, we sought to demonstrate a more modest but clinically important treatment effect, with a 30% reduction in atelectasis incidence (risk ratio, 0.7) from avoidance of nitrous oxide. Based on a type 1 error risk (α) of 5%, with a two-tailed comparison between groups, our projected sample size of 2,600 patients was expected to provide 87.5% power to demonstrate this difference. Incidences were compared using a two-sided chi-square test. Statistical analyses were conducted with Stata 12 (Stata Corp, USA). Given the lower incidence of postoperative pneumonia observed in the earlier ENIGMA trial and the unlikelihood that the current study would have sufficient study power for this comparison, the effect of treatment allocation on the incidence of pneumonia was made a secondary outcome in this *post hoc* study, as was the combination of atelectasis and pneumonia (combined postoperative pulmonary complications). The α threshold for these secondary endpoints was adjusted in line with Bonferroni correction to 1.66%. Hospital length of stay was also compared. The data are presented as mean (SD) for normally distributed data, median [interquartile range] for non-normal data, and *n* (% of total) for categorical data.

Results

Data from 2,328 randomized patients were available for inclusion in the final analysis. At 2 of the 10 sites, digitized data from the first 95 and 175 randomized patients, respectively, were unavailable as digitization of radiological and/or pathology test results had not been implemented by those hospitals up to that point in the trial. Data from a further six randomized patients from the other eight sites were

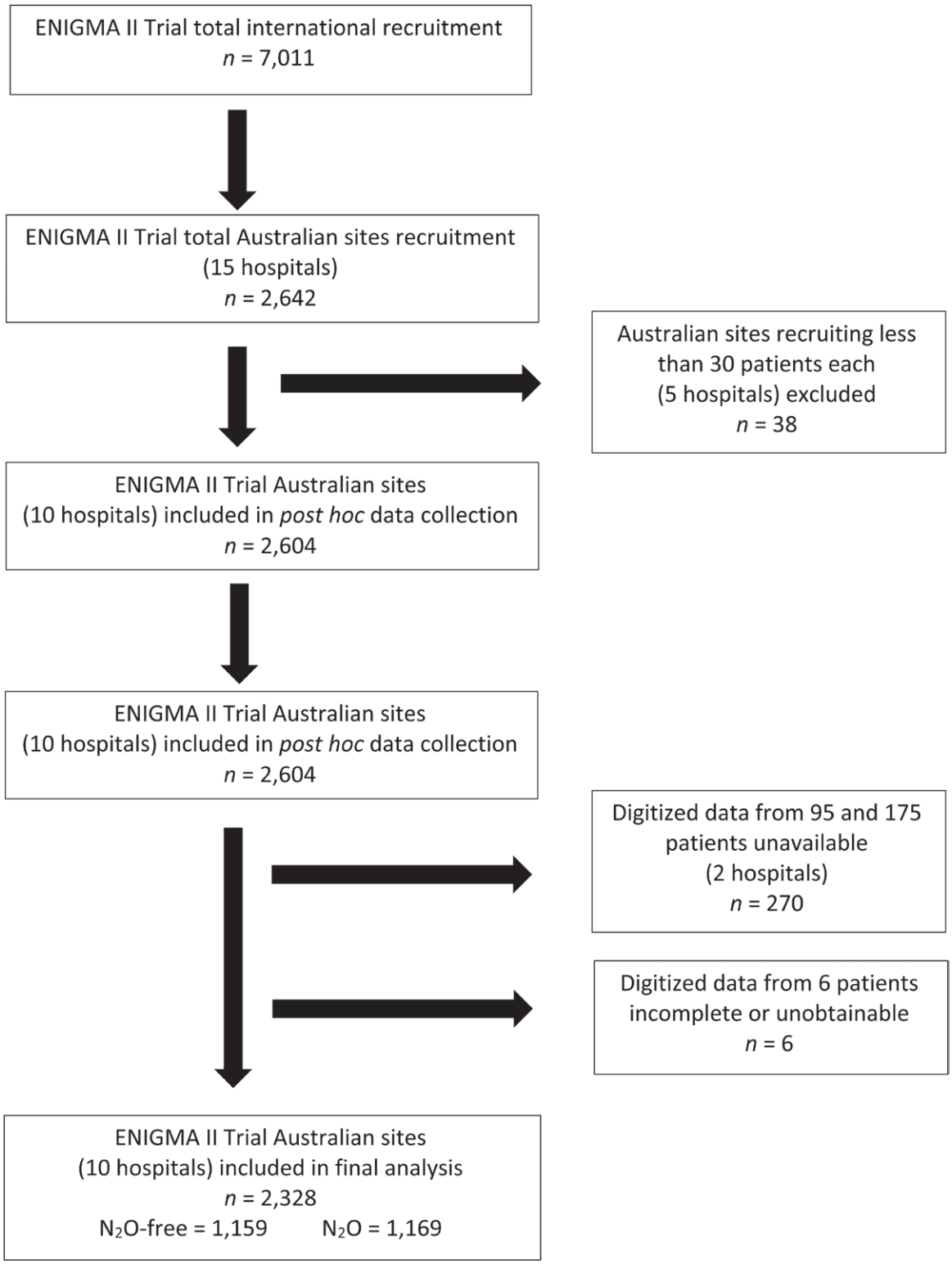

Fig. 1. Flow diagram of inclusion in the study of *post hoc* data collected on patients who were recruited to the Evaluation of Nitrous oxide In the Gas Mixture for Anesthesia (ENIGMA II) trial.

incomplete or unobtainable for the current study and were excluded from the analysis. Figure 1 shows a flow diagram of data inclusion in the final data set. While this effectively reduced the projected study sample size by 276 patients or slightly greater than 10%, recalculated study power was 83%, which was still considered adequate for the purposes of the analysis. This cohort represented 33.2% of the total ENIGMA II trial recruitment.

Table 1 summarizes those demographic and anesthetic management data in the included patients that had been recorded for the ENIGMA II trial. The two groups were similar with regard to type and duration of surgery performed and in recorded risk factors and perioperative management. The difference in delivered concentration (measured as minimum alveolar concentration [MAC] equivalents) of volatile anesthetic agent between the two groups (median [IQR], 0.93 [0.80, 1.06] *vs.* 0.61 [0.45, 0.75]; $P = 0.0001$) reflected the expected contribution of nitrous oxide (approximately one third of total) to MAC in the nitrous oxide group.

Table 2 shows the incidence of postoperative atelectasis and pneumonia in each treatment group. In those patients for whom postoperative pulmonary complications occurred, the median (interquartile range) interval between surgery and diagnostic chest radiology was 1 (0, 3) days. The overall incidence of atelectasis was 16.4%, and that of pneumonia was 4.8%. There was a 19.3% lower incidence of atelectasis with nitrous oxide (171 of 1,169 [14.6%, nitrous oxide group] *vs.* 210 of 1,159 [18.1%, nitrous oxide–free group]; odds ratio, 0.77; 95% CI, 0.62 to 0.97; $P = 0.023$). There was no difference in pneumonia incidence (60 of 1,169 [5.1%, nitrous oxide group] *vs.* 52 of 1,159 [4.5%, nitrous oxide–free group]; odds ratio, 1.15; 95% CI, 0.77 to 1.72; $P = 0.467$) or in combined postoperative pulmonary complications (231 of 1,169 [19.8%, nitrous oxide group] *vs.* 262 of 1,159 [22.6%, nitrous oxide–free group]; odds ratio, 0.84; 95% CI, 0.69 to 1.03; $P = 0.093$). Hospital length of stay [median, interquartile range] was similar between groups (5.2 [3.2, 8.9] days in the nitrous oxide group *vs.* 5.8 [3.3, 9.0] days in the nitrous oxide–free group; $P = 0.314$ on the Wilcoxon rank sum test).

Discussion

Respiratory complications remain among the most common and serious adverse outcomes of major surgery. In the Australian and New Zealand Audit of Surgical Mortality, postoperative pneumonia accounted for 44% of infective complications of surgery.[9] In the U.S. National Surgical Quality Improvement Program analysis of outcomes in 106,000 surgical patients, postoperative pneumonia after colectomy was associated with a tripling of mortality at 1 yr, independent of preoperative patient risk, and was associated with the highest cost of all types of complications studied.[10,11] However, reliable large-trial evidence of effective and practical interventions to reduce the risk of postoperative pulmonary complications in major surgery is still lacking.[4,5] The Multicentre Australian Study of Epidural Anesthesia (MASTER) trial ($n = 888$) showed that the risk of postoperative pneumonia (6.8%) and other complications in abdominal surgery was not significantly improved by perioperative epidural analgesia.[12,13] A variety of techniques for intraoperative lung protective ventilation, such as reduced tidal volume, PEEP, and lung recruitment maneuvers, some of which have improved pulmonary outcomes in the setting of prolonged ventilation and critical care, are still unproven by large trials in the perioperative setting.[14–16]

We found using *post hoc* data collection of pulmonary outcomes that the incidence of atelectasis in the Australian cohort of the ENIGMA II trial was lower with the use of nitrous oxide instead of nitrogen as the balance gas with 30% oxygen in a population undergoing a broad range of major noncardiac surgery. This appears to contradict the findings of the earlier ENIGMA trial, which used an identical protocol for data collection on postoperative pulmonary complications. The ENIGMA trial also studied a population undergoing major noncardiac surgery, although with a smaller proportion of patients undergoing peripheral vascular and endovascular surgery (4% *vs.* 39%) and a higher proportion of abdominal surgery (58% *vs.* 35%) than in the ENIGMA II population, which had a mean age 4 yr older. While the incidence we measured of atelectasis in the nitrous oxide group (14.6%) in ENIGMA II was very similar to that in the nitrous oxide arm in ENIGMA (13%), the 19.3% lower relative risk of atelectasis with nitrous oxide in ENIGMA II stands in sharp contrast to that in ENIGMA, which found a 73% higher risk. These earlier findings were seen as mechanistically consistent with the known propensity of nitrous oxide, which is a soluble inert gas, to promote absorption atelectasis in poorly ventilated lung segments when delivered at high inspired concentrations (greater than 50%)[17,18] and were also seen as consistent with the potential for immunosuppression due to the inhibition of the methionine synthetase system and DNA synthesis by nitrous oxide.[19,20] For this reason, the opposing result of this *post hoc* study of the ENIGMA II trial might be interpreted as a chance finding, given that the analysis was not preplanned and was restricted to the Australian cohort of the ENIGMA II trial. However, the current data have greater statistical power than that of the first ENIGMA trial in detecting a treatment effect on these postoperative outcomes, because of the higher overall incidence of atelectasis and pneumonia in our ENIGMA II sample.

This discrepancy in pulmonary outcomes is paralleled by other key differences in the findings of the two trials. Both trials were assessor-blinded randomized controlled trials, in which only the treating anesthesiologist was aware of the trial treatment allocation. However, ENIGMA II, despite its substantially larger size and statistical power, did not

Table 1. Demographic and Anesthetic Management Data in the Patients Included in the Study

Variable	Treatment Group: Nitrous Oxide (n = 1,169)	Treatment Group: Nitrous Oxide–free (n = 1,159)
Age, yr	71 [64, 77]	71 [64, 77]
Sex, %		
Male	828 (70.2%)	793 (70.5%)
Female	341 (29.8%)	366 (29.5%)
Body weight, kg	81 [70, 92]	81 [70, 92]
BMI, kg/m^2	28.1 [24.7, 31.6]	28.1 [24.8, 31.7]
Hemoglobin preoperative, g/dl	13.5 (1.8)	13.5 (1.7)
ASA Physical Status score		
I	1 (0.1%)	2 (0.2%)
II	269 (23.0%)	273 (23.6%)
III	826 (70.1%)	811 (70.0%)
IV	71 (6.1%)	73 (6.3%)
Exercise capacity ≥ 4 MET	782 (66.9%)	801 (69.1%)
Current smoker (≤ 6 weeks preoperatively)	242 (20.7%)	227 (19.6%)
Chronic obstructive lung disease/asthma	256 (21.9%)	302 (26.1%)
Current infection or fever	43 (3.7%)	54 (4.7%)
Type of surgery		
Colorectal	32 (2.7%)	32 (2.8%)
Gastrointestinal (noncolorectal)	77 (6.6%)	68 (5.9%)
Hepatobiliary	28 (2.4%)	42 (3.6%)
Urology/renal	90 (7.7%)	90 (7.8%)
Gynecology	7 (0.6%)	5 (0.4%)
Laparoscopic	66 (5.6%)	84 (7.2%)
Vascular	555 (47.5%)	541 (46.7%)
Open abdominal	97 (8.3%)	91 (7.8%)
Peripheral/endoluminal/other	458 (39.2%)	450 (38.8%)
Neurosurgery/spinal	126 (10.8%)	143 (12.3%)
Orthopedic	181 (15.5%)	182 (15.7%)
Ear/nose/throat/faciomaxillary	33 (2.8%)	28 (2.4%)
Plastics	24 (2.1%)	15 (1.3%)
Elective	1,131 (96.7%)	1,129 (97.4%)
Contaminated or dirty	50 (4.4%)	59 (5.1%)
Duration of surgery, h	2.7 [1.9, 3.60]	2.6 [1.9, 3.5]
Duration of anesthesia, h	3.1 [2.4, 4.1]	3.0 [2.3, 4.0]
Average intraoperative FIO_2	0.30 [0.30, 0.34]	0.31 [0.30, 0.39]
Anesthetic drugs		
Midazolam	721 (61.7%)	747 (64.4%)
Fentanyl	919 (78.6%)	899 (77.6%)
Morphine	620 (53.0%)	629 (54.3%)
Other opioid	328 (28.1%)	355 (30.6%)
Ketamine	71 (6.1%)	75 (6.5%)
Propofol		
Induction	1,141 (97.7%)	1,129 (97.4%)
Maintenance	46 (3.9%)	39 (3.4%)
End-tidal MAC equivalents volatile anesthetic	0.61 [0.45, 0.75]	0.93 [0.80, 1.06]
Regional/local anesthetic	346 (29.6%)	341 (29.4%)
Antibiotic prophylaxis	1,141 (97.6%)	1,147 (98.9%)
Highest intraoperative SpO_2, %	100 [99, 100]	100 [99, 100]
Lowest intraoperative SpO_2, %	96 [94, 97]	96 [94, 98]
Body temperature at wound closure, °C	36.3 [35.9, 36.8]	36.2 [35.8, 36.6]
Postoperative high dependency unit care	58 (4.9%)	58 (5.0%)
Mechanical ventilation postoperatively	85 (7.3%)	86 (7.4%)

The data are presented as means (SD) for normally distributed data or medians [interquartile range] and *n* (% of total) for categorical data.

ASA, American Society of Anesthesiologists; BMI, body mass index; MAC, minimum alveolar concentration; MET, metabolic equivalents; SpO_2, pulse oximetry hemoglogin oxygen saturation.

Table 2. Primary and Secondary Study Endpoints

Endpoint	Nitrous Oxide Treatment Group (n = 1,169), n (%)	Nitrous Oxide–free Treatment Group (n = 1,159), n (%)	Odds Ratio (95% CI)	Two-sided P Value
Atelectasis	171 (14.6%)	210 (18.1%)	0.77 (0.62, 0.97)	0.023
Pneumonia	60 (5.1%)	52 (4.5%)	1.15 (0.77, 1.72)	0.467
Combined atelectasis and pneumonia	231 (19.8%)	262 (22.6%)	0.84 (0.69, 1.03)	0.093

The statistical comparisons are the odds ratios, 95% CIs, and two-sided p values (chi-square test).

confirm the findings from ENIGMA of a greater incidence of surgical site infection and fever with nitrous oxide.[6,7] As such, our study findings may not seem entirely unexpected. Possible reasons for the differences in outcomes between ENIGMA and ENIGMA II have been discussed previously and include the different protocols for F_{IO_2} in the nitrous oxide–free groups in the two trials.[8] In ENIGMA II, both groups received an F_{IO_2} of 0.3 to control for a possible independent effect of F_{IO_2} on postoperative complications. In contrast, in ENIGMA, the control group was administered an F_{IO_2} of 0.8. This has been suggested as a possible explanation for the lower rate of postoperative pulmonary complications in the control group in ENIGMA, as a hyperoxic ventilation strategy has previously attracted interest in earlier small perioperative trials in reducing pulmonary and septic complications.[21,22] However, the large PeRioperative OXygen fraction – effect on surgical site Infection and pulmonary complications after abdominal surgery (PROXI) trial, which compared postoperative outcomes with an F_{IO_2} of 0.3 *versus* 0.8, failed to show any differences in pulmonary or infective complication.[23] In light of this background, the differences in findings of ENIGMA and ENIGMA II are only made more acute by the addition of our data. A revised formal systematic review of the effects of nitrous oxide on postoperative pulmonary complications incorporating these new large trial data is warranted.[24]

The hypothesis that nitrous oxide anesthesia results in a lower rate of postoperative atelectasis compared to an oxygen–air mix at similar F_{IO_2} might seem implausible for the reasons given above.[17,18] Potential contributors to this finding include the difference observed between the two treatment groups in volatile anesthetic usage. Volatile anesthetics are known to impair lung surfactant and potentiate the action of neuromuscular blockers, both of which might promote postoperative atelectasis in the nitrous oxide–free group. However, the difference between the groups in mean end-tidal volatile anesthetic concentration was only modest (roughly one-third MAC). A further mechanistic basis for our finding, which is worthy of consideration, focuses on the emergence phase of general anesthesia as a period of risk for development of postoperative pulmonary complications after major surgery. There has been longstanding interest, with mixed support from small trials,[25,26] in the proposition that the administration of 100% oxygen during emergence from general anesthesia before extubation, which remains standard clinical practice, promotes clinically significant absorption atelectasis due to rapid washout of alveolar nitrogen from the lung. If so, this could be a substantial contributor to the incidence we found in the nitrous oxide–free group of atelectasis, which then persists into the postoperative period. In the nitrous oxide group, in contrast, where typically 30 to 40 l of nitrous oxide is expected to be stored in body tissues at the end of maintenance phase anesthesia, it can be hypothesized that rapid large volume excretion of nitrous oxide limits collapse of these poorly ventilated lung units during emergence with administration of 100% oxygen. Early rapid nitrous oxide elimination, which predominantly takes place *via* low ventilation–perfusion ratio lung segments due to its relatively low blood solubility (similar to that of desflurane),[27,28] is the basis for the well recognized Fink effect or diffusion hypoxia during emergence from nitrous oxide anesthesia, in which it drives dilution of the other alveolar gases (oxygen, carbon dioxide, and volatile anesthetic), and has been shown to be potent enough to significantly accelerate the elimination of accompanying sevoflurane at the end of anesthesia.[29,30] If this is indeed the explanation for our findings, it reinforces questions about the assumed safety of routinely administering 100% oxygen to intubated patients on emergence and extubation. A large, well powered trial may be warranted comparing atelectasis incidence with that seen after emergence and extubation breathing an enriched oxygen–air mixture instead.

Although our *post hoc* study was not powered to demonstrate a treatment effect on postoperative pneumonia, it has now made the incidence of pneumonia in the ENIGMA II trial available for comparison with other large perioperative trials in patients undergoing major surgery. While there are some differences in the definitions and methodology of data collection between the trials on various interventions in this field, the overall incidence we found of 4.8% was comparable to that observed in a recent large single center trial of low *versus* high tidal volume (3.4%, n = 1,236) in patients undergoing general anesthesia and controlled ventilation for a broad range of major noncardiac surgeries.[14] It was also similar to the multicenter RELIEF trial (3.7%, n = 3,000) but less than that seen in the OPTIMISE trial (10.3%, n = 730), both of which recruited high-risk

patients undergoing abdominal surgery.[29,30] In contrast, in the European high *versus* low PEEP during general anesthesia for open abdominal surgery (PROVHILO, $n = 900$) trial, which recruited patients having open abdominal surgery at increased risk of pulmonary complications according to the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score, 17% of patients overall developed postoperative pneumonia.[15] These differences in incidence most likely reflect the progressively increasing risk of postoperative pulmonary complications between nonabdominal, minimally invasive, and open abdominal surgery populations.

The strength of this *post hoc* study is that the results are based on randomized controlled trial data from a substantial cohort within a large prospective multicenter trial, and data collection was blinded. A limitation is that due to the primary focus of the ENIGMA II trial on perioperative cardiovascular outcomes, some data of relevance to assessment of postoperative pulmonary complication risk, such as ventilatory settings for instance, were not collected at the time and thus not made available for the current study. However, there is little reason to expect that these data would have been significantly different between the treatment groups in the trial. While the *post hoc* nature of the study is a weakness, it nevertheless effectively replicated the protocol of the first ENIGMA trial and a number of other large multicenter trials,[6,14,31,32] in which the instigation of tests (chest x-rays and postoperative pathology and microbiology) was prompted by clinical need according to the judgement of the treating surgical unit, who were blinded to trial treatment allocation. While this is likely to underestimate the incidence of positive radiological findings compared to a trial protocol where chest imaging of all trial participants is mandated, it can be argued that it specifically measures the incidence of clinically significant postoperative pulmonary complications, as well as reduces the exposure of recruited patients to clinically unnecessary postoperative investigation.

For the purposes of comparison as well as the feasibility of *post hoc* data collection, we chose to use an identical definition of postoperative pulmonary complications to that used in the earlier ENIGMA trial. Recently, investigators in the field have sought to arrive at consensus definitions of perioperative trial outcomes, including of postoperative pulmonary complications, to reduce heterogeneity and assist reliable meta-analysis of future trial data.[33] Our definition for atelectasis was the same as that proposed by the Standardised Endpoints and Core Outcome Measures for Perioperative and Anaesthetic Care (StEP-COMPAC) Group.[33] Our definition of pneumonia was different, in that it required a radiological diagnosis with fever and/or leukocytosis but did not follow the U.S. Centers for Disease Control definition, which stipulates clinical symptoms and signs of chest infection and does not include positive sputum microbiology. This provided a binary definition for postoperative pulmonary complication incidence but did not also grade severity on the basis of need for oxygen supplementation or mechanical respiratory support, as recommended by the StEP-COMPAC Group.[33] These criteria should inform the protocols for prospective data collection in future large trials in the field.

In conclusion, *post hoc* collection of data from 2,328 patients recruited to the Australian cohort of the ENIGMA II trial found that in patients undergoing major surgery, inclusion of nitrous oxide was associated with a lower incidence of postoperative lung atelectasis, with no difference in postoperative pneumonia, contradicting the findings of the earlier ENIGMA trial.

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Competing Interests

Dr. Peyton has received funding from Getinge (Solna, Sweden) and Maquet Critical Care (Solna, Sweden) for an unrelated project. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: phil.peyton@austin.org.au. Raw data available at: phil.peyton@austin.org.au.

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