

A Cost-Benefit Analysis of the ENIGMA Trial

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ABSTRACT

Background: The ENIGMA trial was a prospective, randomized, multicenter study that evaluated the clinical consequences of including N₂O in general anesthesia. Patients who were given a N₂O-free anesthetic when undergoing major surgery for which the expected hospital stay was at least 3 days had lower rates of some postoperative complications. This suggests that, despite a higher consumption of potent inhalational agent, there could be a financial benefit when N₂O is avoided in such settings.

Methods: A retrospective cost analysis of the 2,050 patients recruited to the ENIGMA trial was performed. We measured costs from the perspective of an implementing hospital. Direct

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What We Already Know about This Topic

- The ENIGMA trial showed that N₂O-free anesthesia for patients scheduled for major surgery may reduce postoperative complications. It is unknown if this translates into less hospital costs for treatment.

What This Article Tells Us That Is New

- A retrospective analysis of 2,050 patients of the ENIGMA trial shows that the use of more expensive potent inhalational anesthetics is not associated with higher overall costs. The total costs in the N₂O-oxide group were significantly higher compared with the costs of the N₂O-free group.

health care costs include the costs for maintaining anesthesia, daily medications, hospitalization, and complications. The primary outcome was the net financial savings from avoiding N₂O in major noncardiac surgery. Comparisons between groups were analyzed using Student *t* test and bootstrap methods. Sensitivity analyses were also performed.

Results: Rates of some serious complications were higher in the N₂O group. Total costs in the N₂O group were \$16,203 and in the N₂O-free group \$13,837, mean difference of \$2,366 (95% CI: 841–3,891); *P* = 0.002. All sensitivity analyses retained a significant difference in favor of the N₂O-free group (all *P* ≤ 0.005).

Conclusions: Despite N₂O reducing the consumption of more expensive potent inhalational agent, there were marked additional costs associated with its use in adult patients undergoing major surgery because of an increased rate of complications. There is no cogent argument to continue using N₂O on the basis that it is an inexpensive drug.

NITROUS oxide has traditionally been viewed as an inexpensive drug, especially when the additional benefit of reduced requirement for other more expensive anesthetic agents

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is considered. However, this view does not take into account the cost implications of the side effects of N₂O.

We have previously reported the results of the ENIGMA trial.¹ In this study, patients who were given a N₂O-free anesthetic when undergoing major surgery had lower rates of major complications, as well as less severe postoperative nausea and vomiting (PONV). In addition, the patients in the N₂O-free group were more likely to be discharged from the intensive care unit (ICU) on any given day than those in the N₂O group. These findings suggest that a possible financial benefit of avoiding N₂O in the ENIGMA trial exists despite no statistically significant difference in hospital length of stay between groups. A criticism of the ENIGMA trial has been that it failed to acknowledge the costs saved by the use of N₂O to reduce consumption of more expensive alternatives.² The aim of this retrospective analysis therefore was to determine whether there were economically significant differences in the cost of the in-patient stay between the two patient groups in the ENIGMA trial, taking into account the costs of drugs used and adverse clinical outcomes.

Materials and Methods

The ENIGMA trial was a prospective, randomized, multicenter study that analyzed 2,050 patients.¹ Inclusion criteria required patients to be at least 18 yr old, presenting for surgery expected to exceed 2 h and expecting a postoperative stay of at least 3 days. Patients were excluded if they were undergoing cardiac surgery, if one lung ventilation was required, or if the anesthesiologist considered N₂O to be contraindicated. The attending anesthesiologists were advised to administer a gas mixture of 70% N₂O and 30% oxygen in the N₂O group, and 80% oxygen and 20% nitrogen in the N₂O-free group. All other drugs were administered at the discretion of the attending anesthesiologist.

The data collected for the ENIGMA trial included details of the duration of surgery, the time to fitness for discharge

from the postanesthetic care unit (PACU), the fractions of inhaled gases, other anesthetic agents used, and prophylactic as well as therapeutic antiemetics. Severe PONV was defined by two or more episodes of expulsion of gastric contents at least 6 h apart or requiring three or more doses of antiemetic medication. Wound infection was defined by purulent discharge with or without positive microbial culture, or pathogenic organisms isolated from an aseptically obtained microbial culture. Pneumonia was defined by radiologic changes in conjunction with a temperature greater than 38°C, a leukocyte count greater than 12,000/ml, or positive sputum culture. The mean \pm SD durations of surgery and anesthesia were the same in each group, 3.3 \pm 2.0 h and 3.7 \pm 2.0 h, respectively. The main findings of the ENIGMA trial are summarized in table 1.

Costs

Health economic studies use one or more evaluation methods according to the study objectives.³ A cost-minimization analysis is used when the clinical benefits are found to be equivalent, and the aim is to determine which is the most cost-efficient way of achieving a given objective; cost-effectiveness and cost-utility analyses use natural units such as life-years gained (for the former) or quality adjusted life-years (for the latter) to determine the most efficient way of allocating spending; a cost-benefit analysis uses monetary terms to determine whether a given objective should be pursued to a greater or lesser extent.³ Cost minimization, cost-effectiveness, and cost-utility analyses base their evaluations on a single measurable benefit. Cost-benefit analysis allows better alternative use of the resources and is a particularly useful framework for structuring decision-making problems.³ The ENIGMA trial identified several possible outcome benefits of avoiding N₂O, and each of these may affect the cost of hospitalization. We therefore chose to use a cost-benefit analysis in this study.

Table 1. Main Results of the ENIGMA Trial (Modified from Myles *et al.*¹)

Variable	N ₂ O-free Group (n = 997)	N ₂ O Group (n = 1,015)	Adjusted Odds Ratio* (95% CI)	P Value
Severe nausea or vomiting	104 (10)	229 (23)	0.40 (0.31–0.51)†	<0.001
Wound infection	77 (7.7)	106 (10)	0.72 (0.52–0.98)‡	0.036
Fever	275 (28)	345 (34)	0.73 (0.60–0.90)	0.003
Pneumonia	15 (1.5)	30 (3.0)	0.51 (0.27–0.97)	0.040
Atelectasis	75 (7.5)	127 (13)	0.55 (0.40–0.75)	<0.001
Pneumothorax	1 (0.1)	3 (0.3)	—	—
Myocardial infarction	7 (0.7)	13 (1.3)	0.58 (0.22–1.50)	0.26
Thromboembolism	16 (1.6)	10 (1.0)	1.60 (0.72–3.55)	0.25
Blood transfusion	188 (19)	202 (20)	0.96 (0.75–1.21)	0.71
Stroke	1 (0.1)	1 (0.1)	—	—
Awareness	0 (0.0)	2 (0.2)	—	—
Death within 30 days	3 (0.3)	9 (0.9)	0.33 (0.09–1.22)	0.096

Values are expressed as number with percentage in parentheses.

* Adjusted for age, American Society of Anesthesiologists' physical status score, and duration of anesthesia unless otherwise stated. † Adjusted for postoperative nausea and vomiting risk score (see text) and intraoperative antiemetic drug use. ‡ Adjusted for National Nosocomial Infections Surveillance System score (see text), lowest intraoperative temperature, and smoking status.

Costs were measured from the perspective of an implementing hospital. Direct health-care costs include the costs for maintenance of anesthesia (volatile anesthetics or propofol infusion), hospitalization, and medications. Additional visits to other health-care providers (*i.e.*, family practitioner, medical specialist), professional home care, nonhealth care costs such as paid and unpaid help, and indirect costs of absenteeism of paid and unpaid work were not included.

The direct costs of drugs (including intravenous anesthetics) and antiemetics were obtained from the Alfred Hospital's Pharmacy Department and are based on prices in the year 2010. Intravenous drug costs were rounded up to a complete ampoule. A fixed cost was used for antiemetic prophylaxis as complete details of individual drug data were not collected in the original study. The combined use of dexamethasone and generic ondansetron was assumed for this purpose. The acquisition cost of inhalational anesthetics were obtained from previously published figures.⁴

The costs of N₂O, oxygen, and medical air were obtained from the Alfred Hospital's Engineering Department and were cross-checked with two commercial providers' prices and contemporary reported prices in the literature.⁵ Actual recorded inspired and end-expired gas concentrations and duration of anesthesia were used to calculate consumption. We did not collect fresh gas flow data in the ENIGMA trial, and so we assumed a value of 2 l/min for sevoflurane and 1 l/min for both isoflurane and desflurane to reflect common practice in many centers. Subsequent costs of inhalational agents were determined using established formulae.⁶

A literature review was undertaken to determine the costs of complications reported in the ENIGMA trial. A literature search was undertaken using the PubMed database and search terms: "surgical site infection," "pneumonia," "respiratory complications," "intensive care," "postanesthetic care unit" and "recovery room," which were cross-referenced with "postoperative," "costs" and "cost analysis." All searches were limited to adult studies and those published between 1980 and 2010. Non-English language papers were included if results appeared in the translated abstract. Studies deriving costs of complications after cardiothoracic surgery were included in our literature review, despite the exclusion of coronary artery bypass graft surgery from the ENIGMA trial, because the additional costs should be comparable in either case. Studies were excluded if they focused on only part of the postoperative stay (such as ICU stay) or if the focus was on social costs or costs after discharge, which was beyond the scope of the original ENIGMA trial. Studies that incorporated original data from other studies were excluded so as not to double-count cost estimates in our analysis. Studies addressing the cost of PACU and ICU stay were excluded if data were not presented in a "per patient, per day" format and if insufficient data were provided to calculate this cost (see tables 1–5 of Supplemental Digital Content 1, <http://links.lww.com/ALN/A752>). The median from each group of studies was used as the estimate of cost for compli-

cations. For those published studies that incorporated hospital stay in their estimates, we used our attributable cost per day in hospital from the published estimates to more accurately reflect the actual complication costs. All costs are presented in US dollars at September 2010 and were derived from the currency exchange rates at the time of original publication, indexed to inflation from that time.

The drug and median complication costs derived from our literature search and adjustments for current US dollars provided the following estimates used in our analysis:

1. Bulk gas supplies: N₂O \$0.0123 per liter, oxygen and medical air \$0.003 per liter
2. Propofol: \$1.40 per 200 mg ampoule
3. Thiopental: \$12.60 per 500 mg ampoule
4. Inhalational agents (per minimum alveolar concentration hour): sevoflurane \$11.40, isoflurane \$1.50, desflurane \$12.60
5. Prophylactic antiemetic therapy: \$4.95
6. PACU stay: \$0.81 per min (3 studies)^{7–9}
7. PONV (1 or more episodes): \$22.56 (7 studies)^{10–14}
8. Wound infection: \$10,514 (30 studies)^{15–45}
9. Pneumonia: \$13,439 (9 studies)^{16,20–22,27,34,46–48}
10. ICU stay: \$2,110 per day (11 studies)^{49–59}

We did not include intraoperative opioid consumption in our estimates because there was no measurable difference between groups in our original study.¹ Notional costs for atelectasis, pneumothorax, and fever were not included, nor were those endpoints that were not significantly different between the groups (blood transfusion, pneumothorax, myocardial infarction, thromboembolism, stroke, and anesthetic awareness). Total cost thus included the acquisition costs of anesthetic drugs, calculated costs attributed to differences in complications rates, and hospital and ICU stay. Hospital length of stay included the day of surgery.

In Australian hospitals, the average diagnosis-related group funding for a typical major abdominal surgical procedure representative of surgeries undertaken on ENIGMA trial patients is \$12,403 per case. This represents a total estimate of hospital costs per procedure, incorporating both fixed and variable costs. The average costs for an extra day in the hospital vary according to the extent of surgery and the case mix; we used the median value for a selection of diagnosis-related group codings typically used in abdominal surgery, being \$750 per day, and a 5-day hospital stay. This is consistent with published cost data for colonic⁶⁰ and pancreatic⁶¹ surgery. Thus, the episode cost was assumed to be \$8,653 for a 5-day stay, and \$750 per day for each day thereafter. The summed costs attributed with each complication were treated separately.

Economic Evaluation

The aim of the economic evaluation was to determine and compare the total costs for patients receiving either N₂O-free or N₂O-containing anesthesia. We calculated cost-benefit according to published recommendations.^{3,62,63}

Variable costs were used in this analysis because the fixed costs component did not differ between groups (the groups were well balanced for age, sex, American Society of Anesthesiologists physical status, types of surgery, and surgical duration). The net costs were calculated for the primary clinical effect measures of the trial (*i.e.*, adverse outcomes, ICU, and hospital stay). The primary outcome was the net financial savings or loss from avoiding N₂O during major noncardiac surgery.

Sensitivity Analyses

To estimate the uncertainty surrounding the cost estimates, we undertook a sensitivity analysis by replacing our derived costing data with 0.25-fold and fourfold cost substitutions, being approximately the 10th and 90th percentiles of the cost distribution found in all the retrieved costing studies. This was done separately for major complications and ICU and hospital stay.

We explored the effect of including the nonsignificant intergroup differences for pneumothorax, myocardial infarction, and stroke. We chose not to include awareness because of its low rate (incidence, 0.001%) and because we had no data on long-term stress and treatment costs. We then attributed a notional cost for pneumothorax equal to that of pneumonia and used published data for myocardial infarction (\$3,700) and stroke (\$13,000).⁶⁴

Statistical Analyses

The primary analysis included all patients randomly assigned to each group and treated accordingly; that is, a per-protocol analysis. We used actual PACU stay, ICU stay, and hospital stay data for all economic calculations. Patients who died in the hospital had their hospital stay cost calculation based on actual inpatient days (not allocated the maximum value) because there are no additional bed-day costs. Baseline characteristics of the two groups were tabulated using appropriate summary statistics. Analysis of the primary outcome of cost-benefit was performed using a Student *t* test, after testing for equality of variance.^{62,63} In addition, bootstrap methods using 5,000 replicates were undertaken to estimate *P* values and 95% CI for differences in mean costs between the two groups. The bootstrap technique is a computation-intensive resampling method that makes no assumption regarding the underlying population distribution. All *P* values are two-sided. A *P* value of less than 0.05 was considered statistically significant. We used the Statistical Package for Social Sciences-SPSS (Version 18, SPSS Inc. Chicago, IL) for all analyses.

Results

Of the original 2,012 patients in the ENIGMA trial, 12 died within 30 days of surgery (three in the N₂O-free group and nine in the N₂O group); in-hospital deaths limit hospital stay and so reduce costs for these patients.

As previously reported,¹ there were 122 patients in the N₂O-free group (12%) and 140 patients in the N₂O group

Table 2. Demographic and Perioperative Characteristics (Modified from Myles *et al.*¹)

Characteristic	N ₂ O-free Group (n = 997)	N ₂ O Group (n = 1,015)
Age, mean ± SD, yr	56 ± 17	55 ± 16
Male sex, No. (%)	533 (54)	520 (51)
Duration of surgery, hours	3.3 ± 2.0	3.3 ± 2.0
Duration of anesthesia, hours	3.7 ± 2.0	3.7 ± 2.0
ASA physical status		
1	209 (21)	206 (20)
2	548 (55)	557 (55)
3	230 (23)	241 (24)
4	10 (1)	11 (1)
Type of surgery, No. (%)		
General	472 (47)	448 (44)
Colorectal	157 (16)	142 (14)
Neurosurgery	144 (14)	151 (15)
Urology	127 (13)	130 (13)
Orthopedic	86 (8.6)	105 (10)
Gynecology	74 (7.4)	73 (7.2)
Ear, nose, throat, or maxillofacial	40 (4.0)	50 (4.9)
Vascular	40 (4.0)	45 (4.4)
Plastics	14 (1.4)	12 (1.2)
Any abdominal	577 (58)	563 (56)
Propofol infusion	191 (19)	132 (13)
Prophylactic antiemetic	342 (34)	356 (35)

ASA = American Society of Anesthesiologists.

(14%) were admitted to the ICU immediately postoperatively (*P* = 0.30). The median (interquartile range) duration of hospital stay was 7.0 (4.0–10.9) days in the N₂O-free group and 7.1 (4.0–11.8) days in the N₂O group. However, the rate of hospital discharge did not differ between groups (hazard ratio = 1.09; 95% CI, 1.00–1.19; *P* = 0.06). The median duration of ICU stay was 1 day in both groups, but patients in the N₂O-free group were more likely to be discharged on any given day (hazard ratio = 1.35; 95% CI, 1.05–1.73; *P* = 0.02). Rates of severe PONV, pneumonia, and wound infection were higher in the N₂O group.

Table 2 shows the distribution of perioperative characteristics in both groups; additional details can be found elsewhere.¹ Baseline characteristics were comparable in each group. Types of anesthetic techniques and use of prophylactic antiemetic therapy were also comparable.

Total variable costs per patient in the N₂O group were \$16,203 and in the N₂O-free group \$13,837, a mean difference of \$2,366 (95% CI: 841–3,891); *P* = 0.002 (table 3). The parameters most affecting the cost differential between groups are extra bed-days and wound infection. All sensitivity analyses retained a significant difference in favor of the N₂O-free group (all *P* ≤ 0.005) (table 4). The bootstrap technique estimations were comparable, with a mean difference of \$2,366 (95% CI: 844–3,935); *P* = 0.003.

Table 3. Estimated Costs, Rounded to Whole US Dollars, Mean ± SD

	N ₂ O-free Group (n = 997)	N ₂ O Group (n = 1,015)	P Value
Anesthetic drugs*	27 ± 22	26 ± 22	0.16
Bed days†	12,793 ± 11,547	14,685 ± 18,718	0.005
Complications‡	1,017 ± 3,496	1,500 ± 4,210	0.006
Total costs	13,837 ± 13,256	16,203 ± 20,842	0.002

* Includes bulk gas supplies, intravenous induction drug, inhalational anesthetic drug (if used), additional propofol for maintenance of anesthesia (if used). † Includes postanesthesia care unit stay, hospital bed, and intensive care stay. ‡ One or more of: severe postoperative nausea and vomiting, wound infection, or pneumonia.

Discussion

This cost-benefit analysis provides an estimate of the financial burden from the use of N₂O in major surgery. The analysis is from the hospital perspective and is limited to the dollar value of complications that occurred during the first 30 postoperative days, within the boundaries of the original study. Consequently, this analysis addresses neither complications occurring after the original admission nor societal repercussions from lost productivity in the community. It is expected that these theoretic additional costs, if included, would increase the difference between the two study groups as observed in previous reports.¹¹ Furthermore, we did not attempt to place a monetary value on the pain and suffering associated with PONV or other complications.

This analysis has wide applicability. The pragmatic design of the ENIGMA trial allowed the treating anesthesiologists from 19 different institutions to provide their usual anesthetic care for the patient and procedure, apart from the N₂O/oxygen and oxygen/nitrogen variables. Consequently, data in the ENIGMA trial reflect a breadth of anesthetic practice that can be generalized and reliably applied in our cost analysis.

The use of data from previous studies to determine the costs of wound infection and postoperative pneumonia improves the general applicability of this study. Various methods were used in these previous studies, providing cost estimates for the relevant postoperative complications. These methods ranged from prospective direct microcosting techniques to retrospective charge-to-cost conversion based analysis. These methods have their own benefits and limitations, which have been discussed widely, including in the original articles. No discrimination was made in the inclusion of these results based on the methods used in the original studies. However, a sensitivity analysis was undertaken to address any potential limitations.

All of the studies that contributed to the cost estimation of complication used hospital length of stay as a component in their calculation of costs. Hospital stay was the primary endpoint of the ENIGMA trial, and although stay was longer in the group who received N₂O, this finding was not found to be statistically significant (*P* = 0.06). We chose to use the point estimates for length of stay and complication rates for each group, as recommended for cost-effectiveness studies.^{65,66} Because there are overlapping factors that contribute to the costs generated by the management of postoperative complications in addition to length of stay, we chose to exclude hospital stay in the cost calculations for both wound infection and pneumonia. However, those complications not incorporating the cost of hospital stay in their individual cost estimates (PONV, PACU, and ICU stay) were included.

The ENIGMA trial found that, in addition to severe PONV, wound infection, and pneumonia, the incidence of atelectasis or any pulmonary complication was also higher in the patients who received N₂O. Atelectasis was not included in the analysis because there were no precedent studies identified in our literature review that estimated any cost consequences of postoperative atelectasis. We thus assumed there was no cost (unless pneumonia ensued). We ignored the cost of processed electroencephalographic monitoring, including disposable sensors, because of variations in this practice

Table 4. Sensitivity Analyses of the Cost Comparisons, Mean ± SD

	N ₂ O-free Group (n = 997)	N ₂ O Group (n = 1,015)	P Value
Total estimated variable costs (US dollars)	13,837 ± 13,256	16,203 ± 20,842	0.002
Assuming cost estimates of the following as 1/4 that used in the main analysis			
Wound infection	13,228 ± 12,421	15,379 ± 19,902	0.004
Pneumonia	13,686 ± 12,734	15,915 ± 20,136	0.003
Bed-days	4,242 ± 5,301	5,187 ± 7,487	0.001
Assuming cost estimates of the following as fourfold higher than that used in the main analysis			
Wound infection	16,273 ± 18,712	19,500 ± 26,536	0.002
Pneumonia	14,444 ± 16,127	17,356 ± 24,631	0.002
Bed-days	52,218 ± 47,604	60,269 ± 76,765	0.005
Cost estimates if including non-statistically significant complications: pneumothorax, myocardial infarction, and stroke	13,890 ± 13,595	16,303 ± 21,038	0.002

around the world. We also ignored infrastructure costs needed to supply N₂O (bulk gas supplies, piping, anesthetic machine). The cost of processed electroencephalographic monitoring and infrastructure costs are biased against the avoidance of N₂O, and so if these costs are altered they would add further cost to the N₂O group and will not alter our conclusions.

The estimated costs were drawn from studies undertaken in the United States, Canada, Europe, Australia, New Zealand, and Southeast Asia, providing a representative sample of different clinical practices. However, this sample was skewed toward practice in the developed world and is therefore limited in its representation of developing countries. This finding is the result of a lack of health economic studies about postoperative complications conducted in developing countries and identified by our literature review. Use of previous studies to derive cost estimates has limitations. Despite providing a pooled estimate from a variety of health care settings, it may not truly represent the study setting of the original ENIGMA trial, and the magnitude of the complication cost may differ across groups. It does, however, provide data that are more readily generalizable.⁶⁶

An adverse effect of N₂O on severe PONV is the most robust finding of the ENIGMA trial. Several studies^{68–71} have reported that avoiding PONV is a high priority for our patients. Gan *et al.*⁶⁸ found that patients were willing to pay approximately \$100 for an effective antiemetic that would avoid PONV, a finding consistent with that of other studies.^{69,71} Using a cost-benefit rationale, it would seem reasonable to spend up to these values in prophylactic strategies to avoid PONV. Because N₂O is a well-established contributor to PONV risk and a small contributor to the cost of anesthesia, avoidance of N₂O would seem to be a cost-effective strategy in this context.

The concept of a financial burden proportional to PACU length of stay has been disputed previously. Dexter and Tinker⁷² found that the major determinant of PACU costs was the distribution of admissions throughout the day because the costs are primarily the result of wages (98%), which remain constant despite faster recovery, avoidance of PONV, or early discharge. However, the model used by Dexter and Tinker does not consider the cumulative effect of fixed PACU resources if the PACU closes. This is significant from a practical point of view and is an additional financial burden because the cost of operating room time is greater than that of a PACU bed. In addition, the rate of postoperative adverse events proportionally increases the nursing resources needed in PACU.⁷³ Therefore, the speed to suitability for PACU discharge, including the absence of PONV, is a relevant factor in considering PACU costs.

Anesthesiologists now work within an environment of limited resources and increasingly must justify the costs of our clinical decisions. This cost-benefit analysis found that despite the very low acquisition cost of N₂O, there are marked additional costs associated with its use. There is no

cogent argument to continue using N₂O on the basis that it is an inexpensive drug.

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