Prospective Randomized Clinical Trial Comparing Nitrous Oxide and Carbon Dioxide Pneumoperitoneum for Laparoscopic Surgery

Zurab Tsereteli, MD, Maria L Terry, MD, Steven P Bowers, MD, Hadar Spivak, MD, Steven B Archer, MD, Kathy D Galloway, RN, John G Hunter, MD, FACS

BACKGROUND: Recent publications demonstrating the safety and advantages of N_2O for pneumoperitoneum (PP) prompted us to reconsider N_2O as an agent for PP in general surgical laparoscopy. The purpose of this prospective, double-blind, randomized clinical trial was to determine whether N_2O PP has any benefits over CO_2 PP.

STUDY DESIGN: One hundred three patients received N_2O (group I, n = 52) or CO_2 (group II, n = 51) PP for elective laparoscopic surgery. Heart rate, mean arterial blood pressure, end-tidal CO_2, minute ventilation, and O_2 saturation were recorded before PP, during PP, and in the recovery room. Postoperative pain medication use was recorded. Pain was assessed by means of visual analog scale (VAS) at postoperative hours 2 and 4, and on day 1.

RESULTS: There were no differences between groups I and II in patient age, gender, weight, anesthesia risk (American Society of Anesthesiologists Score > 2), operative time, duration of PP, or length of hospital stay. Mean end-tidal CO_2 increase under anesthesia was greater in group II than group I (3.0 versus 0.5 mmHg, $p < 0.001$) despite a greater mean intraoperative increase in minute ventilation in group II than group I (0.7 versus −0.2 L/min $p < 0.001$). The patients who had N_2O PP had less pain 2 hours postoperatively (VAS: 4.9 versus 5.7, $p < 0.05$), 4 hours postoperatively (VAS: 3.3 versus 5.1, $p < 0.01$), and 1 day postoperatively (VAS: 1.7 versus 3.5, $p < 0.01$) than patients who had CO_2 PP. Postoperative narcotic or ketorolac use was not statistically different between groups. There were no adverse events related to either N_2O or CO_2 pneumoperitoneum.

CONCLUSIONS: These results suggest that the use of N_2O PP has sufficient advantages over CO_2 that it should be considered as the standard agent for therapeutic PP. (J Am Coll Surg 2002;195:173–180. © 2002 by the American College of Surgeons)

Initial experience with room air and oxygen as insufflation gases for pneumoperitoneum in laparoscopic surgery reinforced the need for a readily absorbed, noncombustible gas.[1] Nitrogen is poorly soluble, and oxygen may support combustion. Carbon dioxide (CO_2), an odorless gas with diffusion rates across membranes 20 times greater than air, became the most popular substitute for therapeutic pneumoperitoneum. It is inexpensive, extremely soluble in blood, rapidly eliminated by the lungs, and suppresses combustion. Adverse side effects demonstrated with CO_2 pneumoperitoneum include peritoneal irritation, hypercarbia, respiratory acidosis, and cardiac arrhythmias.[2-4] Although these conditions may be tolerated and quickly resolved in healthy people, the elderly and patients with cardiopulmonary dysfunction are placed at greater risk.

Before carbon dioxide, nitrous oxide (N_2O) was the gas preferred by gynecologists for pneumoperitoneum in the 1970s and 1980s.[5,6] Nitrous oxide shares several advantageous properties with CO_2: It is an inexpensive gas, it is rapidly eliminated, and has diffusion and solubility quotients similar to CO_2. It also has anesthetic and an-

No competing interests declared.

Presented at the American College of Surgeons 87th Annual Clinical Congress, New Orleans, LA, October 2001.

Received October 12, 2001; Revised January 25, 2002; Accepted February 12, 2002.

From the Departments of Surgery, Oregon Health and Science University, Portland, OR (Tsereteli, Hunter) and Emory University School of Medicine, Atlanta, GA (Terry, Bowers, Spivak, Archer, Galloway).

Correspondence address: John G Hunter, MD, Department of Surgery, L223, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97201-3098.

Published by Elsevier Science Inc.

ISSN 1072-7515/02/$21.00
PII S1072-7515(02)01194-8

Abbreviations and Acronyms

CO_2 = carbon dioxide
N_2O = nitrous oxide
PP = pneumoperitoneum
VAS = visual analog scale

algesic properties, without the cardiopulmonary side effects of CO_2.[7] But N_2O behaves like air in the presence of high concentrations of combustible gas and electrical charge. It does not suppress combustion, nor does it support combustion, as will high concentrations of oxygen. The "fear factor" engendered by two odd reports describing intraoperative explosions in association with the use of nitrous oxide resulted in a near moratorium on the use of this gas for therapeutic PP despite inconclusive evidence of danger.[8,9] In clinics where use of N_2O was not discontinued, there were no reports of adverse outcomes related to the use of this gas for pneumoperitoneum. Several clinical and experimental studies demonstrated the safety and the advantages of N_2O pneumoperitoneum.[7,10-12] Because it appeared that the real benefits far outweighed the theoretic worries, we wished to reconsider N_2O as an agent for therapeutic pneumoperitoneum in general surgical laparoscopy. The aim of this prospective, double-blind, randomized clinical trial was to determine whether N_2O was equivalent or better than CO_2 when used for therapeutic pneumoperitoneum.

METHODS

The Human Investigations Committee of Emory University approved the study, and informed consent was obtained from all patients. Power analysis revealed that more than 49 patients per group were required to detect a 20% difference in postoperative pain scores. All patients over the age of 21 who were undergoing elective laparoscopic foregut surgery at Emory University Hospital (eg, Nissen fundoplication, Heller myotomy, paraesophageal hernia repair) were offered the opportunity to participate in this trial.

One hundred three patients were randomized to receive N_2O (group I, n = 52) or CO_2 (group II, n = 51) pneumoperitoneum from March 1999 to November 2000 (Table 1).

Patients, anesthesiologists, and pain assessor (ZT) were blinded to the pneumoperitoneum gas used until the patient was discharged from the hospital. Patients were randomized after induction of general anesthesia by an envelope drawing performed by an independent observer who prepared the insufflation gas (KG). Although an attempt was made to blind the surgeon (JGH) to the insufflating gas, differences in insufflation apparatus made this difficult. In no case was the anesthesiologist aware of which gas was being used. All patients underwent preoperative bowel preparation with one bottle of magnesium citrate taken by mouth on the evening before operation, and pneumoperitoneum evacuation at the completion of the procedure was scavenged with a wall suction device to avoid loss of N_2O into the environment. Monopolar electrosurgery and ultrasonic dissection (harmonic scalpel) were used in all operations.

Patients were well matched with respect to demographic information (gender, age, comorbidities, and American Society of Anesthesiologists score). Preoperative evaluation and operative procedures were performed as previously reported [13,14] (Table 1). Three patients (two were from group I, one from group II) were excluded from data analysis because surgical complications rendered postoperative pain assessment and narcotic use far from the range of the laparoscopic procedures (see below). Data were collected and analyzed for the remaining 100 patients, with 50 patients in each group.

Perioperative hemodynamic and respiratory parameters, including heart rate, mean arterial blood pressure, end-tidal CO_2, minute ventilation, peak inspiratory pressure, and oxygen saturation were collected from the anesthesia and hospital records by the first author (ZT). These parameters were recorded at 5- to 15-minute in-

Table 1. Distribution of Laparoscopic Procedures

Procedure	N_2O (n = 52)	CO_2 (n = 51)	n = 103
Nissen fundoplication	43	46	89
Nissen fundoplication with Collis gastroplasty	3	3	6
Heller myotomy	1	—	1
Heller myotomy with Toupet fundoplication	4	—	4
Paraesophageal hernia repair	1	2	3

Table 2. Pre- and Perioperative Characteristics of the Study Population

Variable	N_2O (n = 50)	CO_2 (n = 50)	p Value
Mean age (y, range)	50 (31–69)	50 (28–77)	NS
Gender (F/M)	25/25	26/24	NS
Weight (kg)	82.2 ± 15.9	86.4 ± 14.5	NS
Comorbidities (American Society of Anesthesiologists score > 2)	7 (14%)	9 (18%)	NS
Operative time (min)	147 ± 34	153 ± 35	NS
Duration of pneumoperitoneum (min)	136 ± 33	142 ± 35	NS
Length of stay after operation (d)	1.7 ± 0.6	1.9 ± 0.7	NS

tervals before induction of pneumoperitoneum, during pneumoperitoneum, and in the recovery room. Patients with chronic respiratory or cardiac diseases had arterial or central line placement at the time of operation, as clinically indicated. In one patient with an arterial catheter, additional data included blood pH, PaO_2, and $PaCO_2$. Mean values of all measured parameters were calculated for each time period, and the change in the mean values between time periods was used for statistical analysis (see below).

A patient-controlled analgesic pump for self-administration of intravenous narcotics, including morphine, hydromorphone (Dilaudid), or meperidine (Demerol) (selected in that order preferentially and dependent on patient allergy and sensitivity) was started in the recovery room and continued until a diet was tolerated. At that time the patient-controlled analgesic pump was discontinued and patients were placed on oral analgesic elixir (acetominophen-oxycodone) as needed for comfort. Intravenous ketorolac was used at the discretion of the nurse or at the request of the patient to supplement the patient-controlled analgesia or oral narcotics. The quantities of administered analgesics and narcotics were recorded. Dosage of hydromorphone and meperidine was converted into equivalent units of morphine for statistical analysis. Postoperative pain was assessed by the first author (ZT) using a visual analog scale (VAS) for pain scoring (on a 0 to 10 scale) at 2 and 4 hours after operation and on postoperative day 1. Additional data collected prospectively included operative time, duration of pneumoperitoneum, length of hospital stay after operation, adverse effects of pneumoperitoneum, and complications of surgery.

For statistical analysis, the Student's *t*-test, chi-square test, and the Mann-Whitney U test for nonparametric data were performed using GraphPad InStat statistical program (GraphPad Software Inc, San Diego, CA). A p value < 0.05 was considered to represent a statistically significant difference between groups.

RESULTS

Fifty-two of these patients (N_2O group) received nitrous oxide pneumoperitoneum, 51 patients had carbon dioxide pneumoperitoneum (CO_2 group). The procedure was completed laparoscopically in 102 of 103 patients (99 %) with conversion to laparotomy in one N_2O patient (1%) because of a significant amount of herniated twisted and folded stomach in the mediastinum. Another patient in the N_2O group demonstrated an esophageal leak on routine post-Collis gastroplasty contrast radiograph, which required thoracotomy to repair and extended her hospital stay to 15 days. One patient in the CO_2 group was relaparoscoped on postoperative day 1 because of a herniation of his fundoplication. These three patients were excluded from further data analysis.

The remaining 100 patients, 50 in each group, met all study criteria for data collection. Both trial groups were homogeneous with respect to demographics (age, gender, weight, American Society of Anesthesiologists Score > 2), intraoperative variables (volume of insufflation gas used, duration of operation, duration of pneumoperitoneum), and length of hospital stay after operation (Table 2). There were no statistically significant differences between N_2O and CO_2 groups in the intraoperative heart rate changes, mean arterial blood pressure changes, oxygen saturation changes, and peak inspiratory pressure changes during pneumoperitoneum (Table 3). In contrast, there was a greater mean increase in end-tidal CO_2 partial pressure during pneumoperitoneum in the CO_2 group than in the N_2O group ($p < 0.001$) (Fig. 1), despite more ventilator adjustments increasing minute ventilation (by the anesthesiologist) in the CO_2 group than in the N_2O group ($p < 0.001$) (Fig. 2).

Table 3. Perioperative Hemodynamic and Respiratory Parameters

Parameters	N_2O (n = 50)	CO_2 (n = 50)	p Value
Δ Heart rate (beats/min)	3.4 ± 8.9 ↑	4.0 ± 9.1 ↑	NS
Δ Mean arterial pressure (mmHg)	6.0 ± 9.8 ↑	9.8 ± 11.1 ↑	NS
Δ Oxygen saturation (%)	0.5 ± 1.1 ↓	0.5 ± 0.9 ↓	NS
Δ Peak inspiratory pressure (cm H_2O)	5.6 ± 4.3 ↑	5.9 ± 5.2 ↑	NS

Δ, difference in mean values measured before and during pneumoperitoneum.

There were no adverse events related to either N_2O or CO_2 pneumoperitoneum. Six patients (four with N_2O and two with CO_2) developed intraoperative pneumothorax, and all had intraoperative transhiatal evacuation with a red rubber catheter placed across the diaphragm and evacuated to water seal through a trocar site at the completion of the procedure. In no case was residual pneumothorax seen on postoperative chest radiograph.

Postoperative pain, assessed using a visual analog pain scale, revealed that patients in the N_2O group had significantly less pain than patients in the CO_2 group at postoperative hours 2 (4.9 versus 5.7, $p<0.05$), 4 (3.3 versus 5.1, $p<0.01$), and day 1 (1.7 versus 3.5, $p < 0.01$) (Fig. 3). It appeared that there was less need for postoperative narcotic pain medication in the N_2O group than the CO_2 group, but none of these mean differences was statistically significant: Intravenous morphine (19.8 ± 2.9 mg versus 24.0 ± 3.0 mg, mean ± SEM, p = NS), ketorolac (122.4 ± 10.3 mg versus 125.4 ± 11.9 mg, p = NS), and oral oxycodone (53 ± 12.5 mg versus 69.5 ± 12.5 mg, p = NS).

DISCUSSION

This study demonstrates that nitrous oxide pneumoperitoneum offers several advantages to carbon dioxide pneumoperitoneum, and provides a safe alternative gas for abdominal insufflation in elective laparoscopic operations. As previously reported, postoperative pain is less with N_2O pneumoperitoneum than with CO_2 pneumoperitoneum, and intraoperative ventilator and metabolic management is made simpler by the use of N_2O pneumoperitoneum.[11,15-18]

Undoubtedly, today carbon dioxide is the primary insufflation gas in laparoscopy because of its proved safety, low cost, rapid absorption, and its ability to suppress combustion. But as laparoscopic surgical procedures have advanced in duration and complexity, and are performed on a population that is older and less healthy, complications of CO_2 pneumoperitoneum are more frequent.[2-5,15,16] Complications reported include hypercarbia, acidosis, tachycardia, decreased stroke volume, arrhythmias, hyperventilation-induced barotrauma, oliguria, increased intracranial pressure, and peritoneal irritability.

Although some of these adverse effects might occur with other insufflating gases, only CO_2 risks the development of hypercarbia and respiratory acidosis.[2,3] In healthy individuals, hypercarbia is corrected by increasing minute ventilation, but in elderly patients and those with preexisting cardiopulmonary dysfunction, compensation is not always possible, especially during pro-

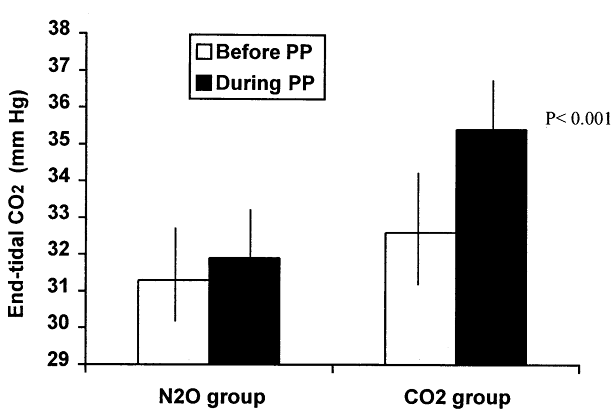

Figure 1. Mean end-tidal CO_2 (mmHg) values during N_2O and CO_2 pneumoperitoneum (PP).

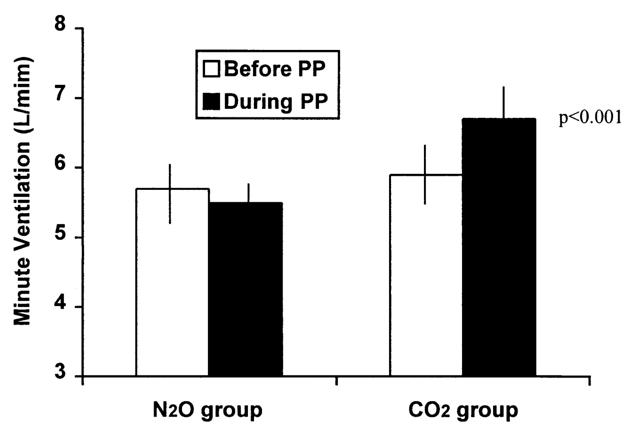

Figure 2. Mean minute ventilation (L/min) values during N_2O and CO_2 pneumoperitoneum (PP).

longed laparoscopic operations.[4,15,19] In a previous large animal study, we demonstrated that end-tidal CO_2 measurement may significantly underestimate arterial pCO_2, and this difference is magnified when a rapid ventilatory rate is required to compensate for respiratory acidosis.[12] For several years, it has been our practice to change insufflation gas to N_2O in patients who develop refractory hypercarbia during laparoscopy with a CO_2 pneumoperitoneum. This study supports the safety of nitrous oxide as the primary insufflation gas in patients with little ventilatory reserve.

In this study and several previous reports, CO_2 pneumoperitoneum creates more pain during and after laparoscopic procedures than N_2O pneumoperitoneum.[16-18] One proposed mechanism for this observation is that carbonic acid, produced when CO_2 dissolves, causes peritoneal irritation.[20,21] A second theory is that the central nervous system anesthetic effects of the absorbed N_2O decrease pain perception. Unfortunately, as a result of limited use of N_2O, clinical trials comparing these two gases are few. The two earliest studies assessed pain associated with diagnostic laparoscopy under local anesthesia. Both studies were randomized and double blind, and both studies demonstrated less postoperative discomfort with N_2O than with CO_2.[16,18] More recently, a prospective randomized study of 40 patients compared N_2O and CO_2 pneumoperitoneum during laparoscopic cholecystectomy. This study demonstrated that N_2O pneumoperitoneum produced less postoperative pain and required a decreased quantity of anesthetic for the surgical procedure than did CO_2 pneumoperitoneum.[17]

The theoretic concern related to the use of N_2O pneumoperitoneum is its inability to suppress combustion when compared with CO_2, or inert gases. N_2O is not combustible, but in the presence of a volatile gas, such as hydrogen or methane, N_2O is an oxidizer with properties similar to room air (20% O_2, 80% N_2) in support of combustion. As a first step toward proving the safety of N_2O pneumoperitoneum, several years ago we demonstrated that even without bowel preparation, methane and hydrogen were undetectable in the pneumoperitoneum of patients undergoing laparoscopic cholecystectomy.[7] Similar findings have been reported in other studies.[10,11] On the other hand, it is theoretically possible for an accidental electrosurgical or laser colotomy in a methane- or hydrogen-filled colon to ignite under N_2O pneumoperitoneum.[22] Hydrogen and methane are produced in the colon by the normal bacterial flora, and are not found elsewhere in the gut if there is no bacterial overgrowth. Fasting does not change methane production but bowel cleansing with nonfermentable substrates (magnesium citrate or polyethylene glycol) reduces both to negligible levels. In early colonoscopic polypectomy cases, the colon was insufflated with CO_2 to avoid combustion. After the beneficial effects of bowel preparation were better understood, CO_2 was abandoned in favor of air to simplify the insufflation apparatus. It seems to make more sense to cleanse the bowel, then to condemn N_2O pneumoperitoneum. Given this extremely low risk scenario, the necessity of bowel cleansing for each N_2O laparoscopic case is debatable. Outside of this study it has not been our practice to cleanse the bowels of all patients undergoing N_2O pneumoperitoneum. A second potential disadvantage of N_2O is bowel distention, seen when N_2O is used as an anesthetic agent. Because the small amount of N_2O absorbed in the circulation is rapidly eliminated by the lungs, this was not a theoretic or practical problem.

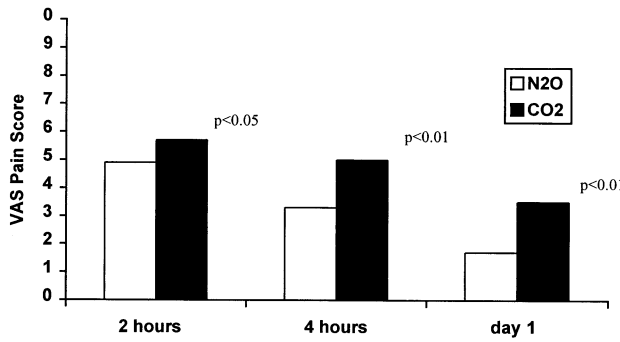

Figure 3. Median visual analog scale (VAS) pain scores in N_2O and CO_2 groups at 2 and 4 hours after operation and on postoperative day 1.

Gastrointestinal injury is a rare complication of laparoscopic surgery, yet it may occur either with insertion of the insufflation needle, umbilical trocar, or during the course of operative dissection. Schrenk and colleagues,[23] in review of 4,672 laparoscopic procedures, reported 10 intestinal perforations (0.2%). Deziel and associates[24] accumulated complication data on 77,604 individuals undergoing laparoscopic cholecystectomy. They noted 12 duodenal perforations (0.015%), 5 gastric (0.006%), 57 small intestinal (0.07%), and 35 colon perforations (0.045%). A review of recent reports of laparoscopic Nissen fundoplications revealed a total of 1,012 procedures with 13 gastrointestinal injures (1.28%). No colon perforations were reported.[25] Assuming the highest reported incidence of accidental colon injury (1 in 2,000) and the requirements for large concentrations of H_2 or CH_3 to be present in the colon, it is no surprise that many hundreds of thousands of laparoscopic tubal sterilization procedures have been performed in the Western world safely in an N_2O environment with monopolar and bipolar electrosurgery without a single episode of combustion.[7,26]

In fact, the literature that created the N_2O "scare" should be revisited. One report emanated from Sri Lanka and the other from Egypt.[8,9] In both cases, combustion occurred after all electrical current had ceased. So it is unlikely that these cases represent ignition of combustible gas with energy applied by a laparoscopic instrument. Similarly, it is unlikely that we will ever be able to discern what really happened with these two cases, but it seems most unreasonable to implicate N_2O.

In conclusion, the use of N_2O as the gas for pneumoperitoneum during elective laparoscopic procedures is safe and has several advantages over CO_2, including less postoperative pain and decreased risk of hypercarbia, a potentially lethal complication of CO_2 pneumoperitoneum when associated with acidosis and arrhythmia. N_2O has enough advantages over CO_2 that it should be the gas of choice for general surgical laparoscopy, especially when prolonged laparoscopic operations are performed on the elderly and on patients with preexisting cardiopulmonary dysfunction.

Practically, the process of changing hospital practice to allow routine use of N_2O pneumoperitoneum may be difficult. Anesthesia and hospital safety manuals are rife with misinformation about the dangers of N_2O. Overcoming the fear factor is the hardest step. Subsequently, the conversion is not difficult. Where standard laparoscopy carts are wheeled to the operating table, it is easiest to dedicate one cart in each operating suite to a nitrous oxide tank. A special connecting cord is inexpensive and nitrous oxide cylinders are inexpensive and ubiquitous in operating suites, but one needs to check with the insufflator manufacturer because some insufflators may need to be adjusted for alternative gases. In endosuites, where hospital-based gases are brought in through the ceiling, it is easy, in the design phase, to bring N_2O to the insufflator through the ceiling-mounted arm. At Emory, a special insufflator was dedicated to N_2O, but in future endosuites at Oregon Health and Science University, hospital system-based N_2O will be brought in through the ceiling.

Author Contributions

Study conception and design: Hunter, Spivak
Acquisition of data: Tsereteli, Galloway, Terry, Archer
Analysis and interpretation of data: Tsereteli, Bowers
Drafting of manuscript: Tsereteli, Bowers
Critical revision: Hunter

REFERENCES

1. Uhlich GA. Laparoscopy: the question of the proper gas. Gastrointest Endosc 1982;28:212–213.
2. Ho HS, Gunther RA, Wolfe BM. Intraperitoneal carbon dioxide insufflation and cardiopulmonary function. Arch Surg 1992; 127:932–938.
3. Scott BB, Julian DG. Observations on cardiac arrhythmias during laparoscopy. Br Med J 1972;1:411–413.
4. Wittgen CM, Andrus CH, Fitzgerald SD, et al. Analysis of the hemodynamic and ventilatory effects of laparoscopic cholecystectomy. Arch Surg 1991;126:997–1001.
5. Minoli G, Terruzzi V, Tadeo G. Laparoscopy: the question of the proper gas [letter]. Gastrointest Endosc 1983;29:325.
6. Robinson JS, Thompson JM, Wood AW. Laparoscopy explosion hazards with nitrous oxide [letter]. Br Med J 1975;2:765.
7. Hunter JG, Staheli J, Oddsdottir M, Trus TL. Nitrous oxide pneumoperitoneum revisited: Is there a risk of combustion? Surg Endosc 1995;9:501–504.
8. El-Kady AA, Abd-Elrazek M. Intraperitoneal explosion during female sterilization by laparoscopic electrocouagulation. Int J Gynecol Obstet 1976;14:487–488.
9. Gunatilake DE. Case report: fatal intraperitoneal explosion during electrocoagulation via laparoscopy. Int J Gynecol Obstet 1978;15:353–357.
10. Drummond GB, Scott DB. Laparoscopy explosion hazards with nitrous oxide. Br Med J 1976;1:586.
11. El-Minawi MF, Wahbi O, El-Bagouri IS, et al. Physiologic changes during CO_2 and N_2O pneumoperitoneum in diagnostic laparoscopy. J Reprod Med 1981;26 338–346.
12. Hunter JG, Swanstrom L, Thornburg K. Carbon dioxide pneumoperitoneum induces fetal acidosis in pregnant ewe model. Surg Endosc 1995;9:272–279.
13. Waring JP, Hunter JG, Oddsdottir M, et al. The preoperative evaluation of patients considered for laparoscopic antireflux surgery. Am J Gastroenterol 1995;90:35–38.
14. Hunter JG, Trus TL, Branum GD, et al. A physiologic approach to laparoscopic fundoplication for gastroesophageal reflux disease. Ann Surg 1996;223:673–687.
15. Holzman M, Sharp K, Richards W. Hypercarbia during CO_2 gas insufflation for therapeutic laparoscopy: a note of caution. Surg Laparosc Endosc 1992;2:11–14.
16. Sharp DB, Wayne PP, Brady CE. Comparison of CO_2- and N_2O-induced discomfort during peritoneoscopy under local anesthesia. Gastroenterology 1982;82:453–456.
17. Aitola P, Airo I, Kaukinen S, Ylitalo P. Comparison of N_2O and CO_2 pneumoperitoneum during laparoscopic cholecystectomy with special reference to postoperative pain. Surg Laparosc Endosc 1998;8:140–144.
18. Minoli G, Terruzzi V, Spinzi GC, et al. The influence of carbon dioxide and nitrous oxide on pain during laparoscopicy: a double-blind, controlled trial. Gastointest Endosc 1982;28: 173–175.

19. Gardner JG, Trus TL, Laycock WS, Hunter JG. Converting from carbon dioxide to nitrous oxide pneumoperitoneum. Surg Endosc 1995;9:1034–1035.
20. Nyerges A. Pain mechanism in laparoscopic surgery. Semin Laparosc Surg 1994;1:215–218.
21. Phillips RS, Goldberg RI, Watson PW, et al. Mechanism of improved patient tolerance to nitrous oxide in diagnostic laparoscopy. Am J Gastroenterol 1987;82:143–144.
22. Neuman GG, Sidebotham G, Negoianu E, et al. Laparoscopy explosion hazards with nitrous oxide. Anesthesiology 1993;78:875–879.
23. Schrenk P, Woisetschlager R, Reiger R, Wayland W. Mechanism, management and prevention of laparoscopic bowel injury. Gastrointest Endosc 1996;43:572–574.
24. Deziel DJ, Millikan KW, Economou SG, et al. Complications of laparoscopic cholecystectomy: a national survey of 4292 hospitals and an analysis of 77,604 cases. Am J Surg 1993;165:9–13.
25. Spivak H, Lelcuk S, Hunter JG. Laparoscopic surgery of the gastroesophageal junction. World J Surg 1999;23:356–367.
26. Sodestrom RM. Dangers of nitrous oxide pneumoperitoneum. Am J Obstet Gynecol 1976;124:668–669.

Invited Commentary

Theodore N Pappas, MD, FACS
Durham, NC

When I review a manuscript of a prospective randomized trial, I evaluate it based on several criteria. First, does the study ask a good question; second, is the patient population correct for this study; third, is the study designed correctly; fourth, are the endpoints clearly defined; and finally, are the conclusions supported by the data.

Dr Hunter and his colleagues have asked a very important question as to whether CO_2 or NO_2 is the ideal insufflation agent. The word *better* is the key. The criteria for *better* in this study are pain, safety, and hemodynamics. Another question not answered by this study is cost. Have the authors evaluated cost of an alternate insufflation system for all or part of the laparosocpic cases in a hospital?

I am a little worried about the study population. The authors included anyone who would agree to the study, not just high-risk patients. The authors state that NO_2 is safer than CO_2, yet their data show they have the same safety profile as defined by the study. The study implies that the increased CO_2 levels measured translate to higher risk for patients with severe lung or heart disease. Unfortunately, their patient population is not described as high risk and cannot be used to support this contention. Should a study be designed to look specifically at high-risk patients?

I think the study design to evaluate postoperative pain is quite good. I was surprised that the authors did not show a difference in narcotic use. Do they think the study is underpowered for this endpoint? If the patients say there is more pain but they don't medicate themselves for it with a patient-controlled analgesia machine, is this "important pain?" In other words, did the differences they show really make a difference?

Injection of local anesthetic before incision has been shown to reduce the pain of laparoscopic surgery. I understand the authors did not study this issue, but can they conjecture whether a local anesthetic would have had the same effect on pain that NO_2 did?

If the authors had to redesign the study now with retrospective glasses on, would or could they change the safety endpoints to better make their point on the relative safety of NO_2 versus CO_2?

Finally, I think the authors' conclusions go far beyond your results. Their study shows there is a statistically significant difference in pain but not pain medications, still a conclusion about pain seems reasonable. No conclusions can be made about safety, because the study was not powered for safety issues. Given the small incidence of complications attributable to either of these agents, a conclusion along these lines does not seem reasonable. How many patients do the authors estimate would be required to show differences in "safety?" Thank you for the privilege of allowing me to review this article.

Reply

John G Hunter, MD, FACS
Portland, OR

I wish to thank Dr Pappas for his thoughtful questions about this manuscript.

The cost of a tank of N_2O is no different from the cost of a CO_2 cylinder. An N_2O-specific connection cord to a standard insufflator costs less than $100. In newer "endo suites," the gas from the hospital systems is brought directly to the back of the insufflator. Fortunately, most modern hospitals provide operating rooms with a centralized supply of CO_2 and nitrous oxide piped in through the wall. In the future, the change from N_2O to CO_2 will require nothing more than the flip of a toggle switch. But, because we are unable to identify any disadvantages of using N_2O, I envision that this