Nitrous oxide and risk of surgical wound infection: a randomised trial

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Summary

Background **Nitrous oxide inactivates vitamin B12 and methionine synthase, thereby impairing DNA formation and, consequently, new cell formation. The gas also inhibits methionine production, which can reduce scar formation and depresses chemotactic migration by monocytes. Therefore, we assessed whether nitrous oxide increases the incidence of surgical wound infection.**

Methods **We recruited 418 patients aged 18–80 years, scheduled for colon resection that was expected to last more than 2 h, at three hospitals in Austria and Hungary. Patients were randomly assigned 65% intraoperative nitrous oxide (n=208) or nitrogen (n=206), with remifentanil and isoflurane. The primary outcome was the incidence of clinical postoperative wound infection, analysed by intention to treat.**

Findings **206 patients in the nitrous oxide group and 202 in the nitrogen group were included in the final analysis. Duration of surgery was longer in the nitrogen group (3·4 h [1·5]) than in the nitrous oxide group (3·0 h [SD 1·3]) and arterial pressure (84 mm Hg [10] *vs* 81 mm Hg [9]), bispectral index values (53 [9] *vs* 44 [8]), and end-tidal isoflurane concentration (0·64% [0·14] *vs* 0·56% [0·13]) were greater in patients given nitrogen than in those given nitrous oxide. Infection rate was 15% (31/206) in patients given nitrous oxide and 20% (40/202) in those given nitrogen (p=0·205). Additionally, the ASEPSIS wound healing score, wound collagen deposition, number of patients admitted to critical care unit, time to first food ingestion, duration of hospital stay, and mortality did not differ between treatment groups.**

Interpretation **Nitrous oxide does not increase the incidence of surgical wound infection.**

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Introduction

Wound infections are a frequent and serious complication of anaesthesia and surgery and can prolong hospital stay by 5–20 days per infection,[1] substantially increasing the cost of care.[2] Major factors affecting the incidence of surgical wound infections include site and complexity of surgery,[3] underlying illness (including treatment with immunosuppressive drugs),[2] timely administration of prophylactic antibiotics,[4] intraoperative patient temperature,[1] hypovolaemia,[5] and tissue oxygen tension.[6] Type of anaesthesia can also affect infection risk. Nitrous oxide has been used for more than a century and probably remains the most commonly used general anaesthetic. The gas has been given to several billion surgical patients. However, use of nitrous oxide has decreased in recent years, especially in Europe, and piped-in nitrous oxide is no longer provided in some new hospitals. Among the concerns about nitrous oxide are three properties that suggest that this gas might reduce resistance to surgical wound infection.

The first concern comes from in-vitro evidence indicating that exposure to nitrous oxide inactivates vitamin B12 and thus methionine synthase.[7] Methionine synthase is the enzyme responsible for conversion of homocysteine to methionine and methyltetrahydrofolate to tetrahydrofolate, which are critical pathways for thymidine formation, which, in turn, is essential for DNA formation. Even after brief periods of nitrous oxide administration, DNA synthesis remains abnormal until the fourth postoperative day and does not return to normal until the sixth day.[8] This change restricts formation of new cells, including haemopoietic cells critical for fighting infection. Inhibition of methionine synthase could explain the link between nitrous oxide exposure and spontaneous abortion.[9]

The second concern is that nitrous oxide inhibits methionine production, which in turn reduces protein formation.[10] Without functioning methionine synthase, protein cannot be produced. Protein expression is a critical aspect of scar formation and tissue repair.[11] Thus, nitrous oxide toxicity could impair healing. Consistent with this theory, nitrous oxide administration has been implicated in development of sepsis.[12]

The third disconcerting property of nitrous oxide is that the gas depresses chemotactic migration by monocytes, apparently by interfering with microtubules.[13] By contrast, inhalation of 65% nitrous oxide for as little as 60 min significantly increases polymorphonuclear neutrophil chemotaxis.[14] Chemotaxis is a key part of the bacterial killing process, which needs chemotaxis, phagocytosis, and killing.[15] Which of these components dominates the process and the clinical consequences of these in-vitro observations remains unclear.

The effect of nitrous oxide on surgical wound infections has been investigated previously. However, the study involved patients at low risk of infection and

was thus underpowered for this particular outcome. Furthermore, oxygen concentration, which is an important confounder,[6] was not controlled for.[16] That this investigation did not identify an adverse effect is therefore insufficient reason to conclude that nitrous oxide has no effect on infection. We therefore assessed whether incidence of surgical wound infection is greater in patients given 65% nitrous oxide than in those given 65% nitrogen during elective colon surgery.

Methods

Patients

With the approval of the institutional review boards of each centre, we recruited 418 patients, with American Society of Anesthesiologists (ASA) physical status I–III, scheduled for elective colon resection expected to last more than 2 h, from two hospitals in Austria and one hospital in Hungary. The study was restricted to colon resection because the risk of wound infection is high in these patients.[17] All patients gave written informed consent and were aged 18–80 years. Anaesthesia residents, Outcomes Research fellows, or attending anaesthetists enrolled patients; none of these doctors were involved in patient postoperative care or follow up.

Patients with acute bowel obstruction or those having minor colon surgery (eg, polypectomy, isolated colostomy) were excluded. However, we admitted patients undergoing restorative rectal resection and abdominoperineal excision of the rectum, which carries a particularly high risk of surgical-site infection. Patients in whom the surgeon did not anticipate primary wound closure were excluded, as were those with a history of fever or infection within 24 h of surgery.

Procedures

All patients received standard mechanical bowel preparation with an electrolyte solution the night before surgery. Intraluminal antibiotics were not used. Per surgical routine, cefuroxime (1·5 g) and metronidazole (1·5 g) were given intravenously during anaesthetic induction. Additional antibiotics (eg, to treat clinically suspected infections) were administered according to the judgment of the attending surgeon. Anaesthetic management was standardised. Thiopental sodium (3–5 mg/kg) or propofol (2–3 mg/kg), fentanyl (1–3 μg/kg), and vecuronium (0·1 mg/kg) or rocuronium (0·6 mg/kg) were used for induction; anaesthesia was maintained with isoflurane (0·6%) in 65% nitrous oxide or nitrogen, with vecuronium or rocuronium. An infusion of remifentanil (0·2 μg kg^{-1} min^{-1}) was subsequently started. After induction of anaesthesia, research fellows or attending anaesthetists, who were not involved in data collection, allocated patients to one of two groups. The assignments were based on computer-generated random numbers that were kept in sealed, sequentially numbered envelopes until used. Patients were not informed of their group assignments.

All patients were given 35% inspired oxygen during surgery, which was balanced by either 65% nitrous oxide or nitrogen, until immediately before extubation whereupon 100% oxygen was given. During the first hour of recovery, oxygen was given by nasal prongs at a rate of 2 L/min. Patients in both treatment groups subsequently breathed ambient air unless additional oxygen was needed to maintain oxygen saturation at 95% or more.

The anaesthetist was not blinded to treatment. However, great care was taken to prevent the surgeons from observing the administered gas mixture. Irrespective of group assignment, oxygen was given as necessary to maintain oxyhaemoglobin saturation (S_aO_2) at 95% or more in all patients. Isoflurane and remifentanil doses were adjusted by the attending anaesthetist with the goal of maintaining mean arterial blood pressure at 90% of the pre-induction value. Ventilation was mechanically controlled to maintain end-tidal carbon dioxide tension near 35 mm Hg.

We gave around 12 mL kg^{-1} h^{-1} of crystalloid fluid throughout surgery. Additionally, blood loss was replaced with crystalloid fluid at a 4:1 ratio or colloid fluid at a 2:1 ratio. Crystalloid fluid was administered at 3·5 mL kg^{-1} h^{-1} for the first 24 h after surgery and at 2 mL kg^{-1} h^{-1} for the subsequent 24 h. Intraoperative core temperature was maintained near 36°C.

Target minimum haematocrit was determined prospectively based on the patient's age and cardiovascular status. The target haematocrit was 26% in patients younger than 65 years without significant cardiovascular disease; 28% in patients either 65 years or older or those with significant cardiovascular disease; and 30% or more in patients 65 years and older with significant cardiovascular disease. Leucocyte-depleted allogeneic blood was given as necessary to maintain target haematocrit.

Patient-controlled analgesia with the opioid piritramide was provided postoperatively. Nausea and vomiting were treated with ondansetron (4 mg intravenously). After giving the report to the post-anaesthesia care nurse, the attending anaesthetist sealed the anaesthesia record in an envelope marked with "Anaesthesia Record. Do not open unless necessary for clinical care until 16 days after surgery." Thus, the surgeons and investigators were unable to determine group assignment.

Surgical wounds were examined daily by a physician unaware of group assignment. After discharge, patients were assessed during their 2-week clinic visits. Patients not returning to clinic were contacted by phone by an investigator unaware of group assignment. Preoperative morphometric characteristics, laboratory values, and historical factors that might have affected wound healing or resistance to infection were recorded. Core temperatures were measured in the distal oesophagus during surgery and orally on each subsequent hospital

day. Heart rate and arterial blood pressure were recorded at 15-min intervals during anaesthesia, at 30-min intervals during the first postoperative hour, and then daily throughout the hospital stay. End-tidal isoflurane, nitrous oxide, and carbon dioxide concentrations were measured at 15-min intervals during anaesthesia. The bispectral index was recorded at 15-min intervals with an A1050 monitor (Aspect Medical Systems, Newton, MA, USA).

Patients rated their severity of nausea 2 h after surgery using a 100 mm long visual analogue scale. The number of emetic episodes was simultaneously recorded, along with the need for anti-emetic medication. Time to first flatus and first bowel movement, as well as time to first tolerated liquid and solid oral intake, were recorded. We assessed risk of infection using the Centers for Disease Control and Prevention (CDC) SENIC score, where one point each is assigned for three or more diagnoses, surgical duration 2 h or more, abdominal site of surgery, and the presence of a contaminated or dirty infected wound.[3] We slightly modified the score by our use of admission, rather than discharge, diagnoses. Infection risk was further quantified using the national nosocomial infection surveillance system (NNISS), with which risk was predicted on the basis of type of surgery, ASA physical status rating, and surgical duration.[17]

Primary outcome was the incidence of clinical postoperative wound infection. Wounds were suspected of being infected when pus could be expressed from the surgical incision or aspirated from a loculated mass inside the wound. Samples of pus were obtained and cultured for aerobic and anaerobic bacteria; wounds were deemed infected when the culture was positive for pathogenic bacteria. We also used a slight modification of the 1992 revision of the CDC criteria to diagnose wound infection.[3] However, we modified the criteria by restricting the diagnostic period to 15 days rather than 30 days. Wounds were numerically scored for infection with the ASEPSIS system.[18] This is an established and validated system derived from the weighted sum of points assigned for the following factors: 1) duration of antibiotic administration; 2) drainage of pus under local anaesthesia; 3) debridement of the wound under general anaesthesia; 4) serous discharge; 5) erythema; 6) purulent exudate; 7) separation of deep tissues; 8) isolation of bacteria from discharge; and 9) hospital stay exceeding 14 days.

In a subgroup of 52 patients at the University of Vienna (21 of whom were given 65% nitrous oxide), wound collagen and protein deposition were assessed.[19] Near the end of surgery, a 7 cm long expanded polytetrafluoroethylene implant (Impra, International Polymer Engineering Inc, Tempe, AZ, USA) was inserted into the subcutaneous tissue a few centimetres lateral to the surgical incision. On the seventh postoperative day, the implants were removed and assayed for hydroxyproline and protein.[20]

Statistical analysis

Logistic regression with data from a previous study of patients undergoing elective colon resection[1] suggested that infection rate (as defined by pus and a positive culture) is about 9% in patients maintained at a core temperature of 36ºC. Our study was thus powered to detect a doubling of the infection rate to 18%. We calculated that 500 patients would provide 80% power to detect a statistically significant effect of nitrous oxide at an alpha level of 0·05. We therefore planned to enrol a total of 500 patients with the data and safety monitoring board to review the results after enrolment of 300 and 400 patients.

Morphometric and perioperative data were compared with unpaired, two-tailed, *t* tests for continuous data or χ^2 tests for categorical data. A p value less than 0·05 was regarded as statistically significant. Data are presented as number (%), median (quartiles), or mean (SD). Logistic regression was used to control for covariance that differed between the two treatment groups by $p \leq 0{\cdot}25$, and for blood transfusion, ASA, SENIC, and NNISS scores. Analyses were completed on an intention-to-treat basis.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

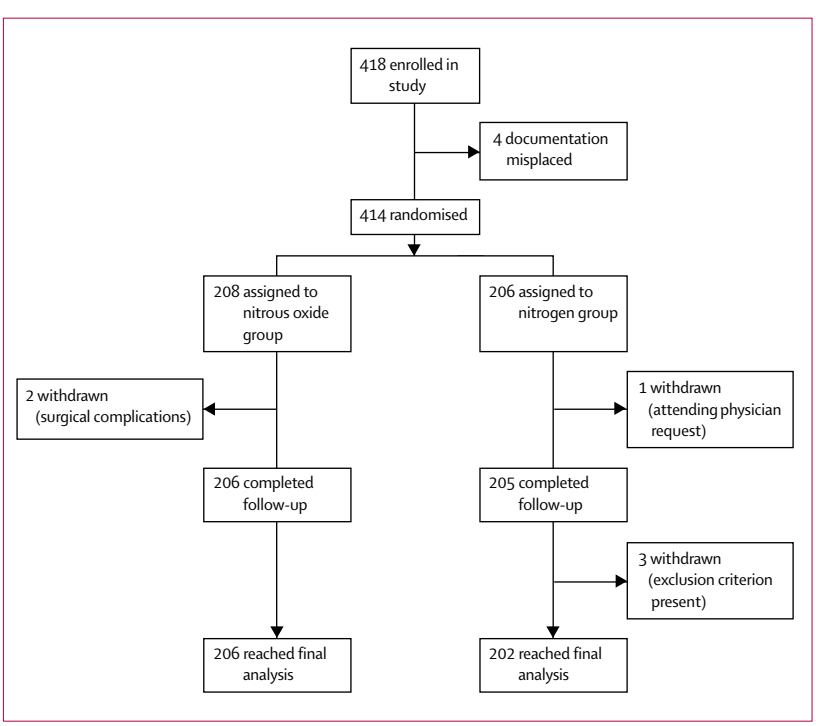

Figure: **Trial profile**

	Nitrous oxide	Nitrogen	p
Number of patients	206	202	..
Number of men/women	103/103	116/86	0·122
Age, years	57 (15)	60 (14)	0·036
Weight, kg	72 (14)	74 (16)	0·234
Height, cm	170 (9)	169 (10)	0·576
Smoker, yes/no	48/155	32/157	0·099
Diabetes	15	22	0·204
Diagnosis			0·403
Cancer	60%	53%	
Inflammatory bowel disease	33%	41%	
Other	7%	6%	
Operative site			0·898
Colon	86%	86%	
Rectum	14%	14%	
Haemoglobin, g/dL	11·3 (8·9)	11·5 (10·4)	0·839
ASA rating			0·563
I	59	50	
II	81	83	
III	42	47	
IV	0	1	
SENIC* score			0·143
1	44	38	
2	145	135	
3	17	29	
NNISS† score			0·383
1	72	59	
2	83	88	
3	22	27	
Infection rate predicted by NNISS	11·8%	12·4%	..

Data are mean (SD), number of patients, or %. *CDC's study on the effect of nosocomial infection control. †National nosocomial infection surveillance system.

Table 1: **Patient characteristics**

Results

Based on an analysis of the first 400 patients, the Data and Safety Monitoring Board stopped the study after concluding that additional enrolment was unlikely to alter the outcome. During their analysis, an additional 18 patients were enrolled. Under intention-to-treat rules, these patients were retained (figure). Of the 418 patients who consented, ten were not included in the data analysis for the following reasons. The data cover sheets were lost for four patients; thus, their group assignment was unknown. Surgical complications occurred in two patients in the nitrous oxide group that required stopping the study. Four patients in the nitrogen group were excluded from the analysis: one patient was excluded when the attending physician refused to allow the patient to participate; the other three patients that were excluded did not meet the inclusion criteria. Thus, 206 patients were included in the nitrous oxide group and 202 in the nitrogen group in the final data analysis; all these patients completed the trial. Patients were enrolled from Nov 10, 1998, until Nov 7, 2002.

The mean nitrous oxide concentration in patients assigned this gas was 64% (SD 5%). Intraoperative oxygen saturation averaged 98% (1%) in each group. Patient characteristics were closely similar in the two groups (table 1). The number of patients needing blood transfusions, the end-tidal partial pressure of carbon dioxide (PCO_2), the average intraoperative core temperature, and the amount of fluids given during surgery did not differ between groups. The duration of surgery was slightly longer in the nitrogen group, whereas the end-tidal isoflurane concentration, mean arterial pressure, and bispectral index values were slightly less in the patients given 65% nitrous oxide than those given nitrogen. Although both groups consumed a similar amount of piritramide during the 2 h after surgery, the pain scores were greater in the nitrous oxide group than in the nitrogen group (table 2).

The incidence of infection, as determined by pus and a positive culture, was 8% in patients given 65% nitrous oxide and 11% in patients given nitrogen. The incidence of infection, as determined by CDC criteria, was also similar in the patients given nitrous oxide or nitrogen (table 3). Logistic regression analysis did not identify any differences in infection risk (table 4). With the combined criteria of infection diagnosed by either pus and a positive culture or CDC criteria, and given the numbers analysed at the end of the study (206 in the nitrous oxide group and 202 in the nitrogen treatment group), there was 80% power to detect a 13% point increase (nitrogen group 20% *vs* nitrous oxide group 33%) and 90% power to detect a 15% point increase (nitrogen group 20% *vs* nitrous oxide 35%). Additionally, the ASEPSIS score; wound collagen deposition; number of patients admitted to the intensive care unit; times to first solid food, flatus, and bowel movement; duration of hospital stay; and mortality were similar in each group (table 3).

Nausea or vomiting during the first 2 h after surgery was observed in 42% of patients given nitrous oxide and 43% of those given nitrogen (p=0·874). However, median VAS scores for nausea were significantly greater in the nitrous oxide group than in the nitrogen group (table 3).

	Nitrous oxide	Nitrogen	p
Hospital			0·540
University of Vienna	156	157	
Donauspital/ SMZ-Ost, Vienna	26	28	
University of Debrecen	24	17	
Duration of surgery, h	3·0 (1·3)	3·4 (1·5)	0·009
Blood transfusions			
Patients	54	62	0·316
Units	122	155	..
Units per patient receiving transfusion	2·3 (1·3)	2·5 (1·5)	0·371
End-tidal PCO2, %	32 (2)	32 (2)	0·434
Intraoperative core temperature, °C	35·9 (0·5)	36·0 (0·5)	0·136
Intraoperative fluids, L	3·9 (1·5)	4·0 (1·8)	0·714
End-tidal isoflurane, %	0·56 (0·13)	0·64 (0·14)	<0·0001
Arterial blood pressure, mmHg	81 (9)	84 (10)	<0·0001
Bispectral index	44 (8)	53 (9)	<0·0001
Duration prophylactic antibiotics, days	4·9 (2·2)	5·2 (2·2)	0·338
Piritramide,* mg	9·0 (6·4)	9·3 (8·0)	0·676
Pain, mm on a VAS†	46 (31)	38 (30)	0·014

Data are mean (SD) or number of patients. *Measured 2h after surgery. †Measured 2h after surgery with the visual analogue scale for pain: 0 mm=no pain; 100 mm=worst imaginable pain.

Table 2: **Perioperative management**

Discussion

With the combined criteria of infection diagnosed by pus and a positive culture or CDC criteria, the incidence of infection did not differ significantly between patients given nitrous oxide and those given nitrogen. Additionally, the ASEPSIS wound healing score, wound collagen deposition, number of patients admitted to critical care units, time to first solid food, duration of hospitalisation, and mortality were similar in the two treatment groups.

Perioperative factors, including anaesthetic management, affect infection risk.[21] For example, maintaining perioperative normothermia reduces infection risk three-fold,[1] and supplemental oxygen halves this risk.[6] Conversely, local administration of epinephrine, which reduces tissue perfusion, increases infection risk when given within several hours of contamination, but not when given later.[22] There were thus reasons to believe that intraoperative exposure to nitrous oxide, a drug thought to impair wound healing and immune response via three mechanisms, might increase the incidence of postoperative infection. However, infection rates in our study did not differ between patients given intraoperative nitrous oxide and those given nitrogen, and this finding was true whether infection was defined by the presence of pus and positive culture or by CDC criteria. The study was adequately powered to detect a clinically important treatment effect, had one existed. We thus conclude that nitrous oxide administration does not substantially increase infection risk.

Our results are consistent with previous (underpowered) attempts to link nitrous oxide to infection risk,[23,24] suggesting that any effect of nitrous oxide on wound infection risk is relatively small compared with other perioperative factors such as body temperature, oxygen administration, prophylactic antibiotics, glucose control, and surgical site preparation. Taken together, available data do not support a policy of avoiding nitrous oxide use to reduce the incidence of postoperative wound infection. The 11% infection rate observed here, defined by expression of pus that was culture-positive for pathogenic bacteria in the patients given nitrogen is identical to the infection rate reported in a previous group of colon-resection patients given 30% oxygen in nitrogen.[6] That our overall infection rate, which combined pus and a positive culture with CDC criteria, was greater simply indicates that the CDC criteria are less strict than those we have used in previous similar studies.[6]

2 years after our study started, we showed that supplemental oxygen (80% *vs* 30%) halves the risk of surgical wound infection.[6] However, it is impossible at atmospheric pressure to simultaneously administer useful concentrations of nitrous oxide, a weak anaesthetic,[25] and supplemental oxygen. It was therefore imperative that our control patients be given nitrogen rather than oxygen. The institutional review boards at each participating hospital agreed that informed patients could continue to participate in the study using the original design.

We have previously reported in a subset of 344 patients that moderate-to-severe bowel distension occurs in 23% of patients given nitrous oxide, but in only 9% of those given nitrogen ($p<0\cdot001$).[26] Although our results are consistent with previous reports,[27] they contrast with others.[28] However, all the studies that did not identify a significant effect of nitrous oxide on bowel distension were seriously underpowered. Our results indicate that the number-needed-to-harm for a case of moderate or severe bowel distension from nitrous oxide was seven (95% CI 5–13). Although significant, this incidence of bowel distension was insufficient to make the investigators or surgeons aware of group assignment.

	Nitrous oxide	Nitrogen	p
Infection diagnosed by pus and positive culture	17 (8%)	23 (11%)	0·287
Infection diagnosed by CDC criteria			
Superficial	28 (14%)	34 (17%)	0·362
Deep	9 (4%)	13 (6%)	0·355
Peritoneal	2 (1%)	6 (3%)	0·145
Any CDC infection	30 (15%)	38 (19%)	0·250
Total infection by either criteria*	31 (15%)	40 (20%)	0·205
ASEPSIS† score	5·6 (10·1)	7·4 (13·5)	0·137
Wound collagen deposition, ng/mm‡	1·4 (0·7)	1·4 (0·7)	0·683
Intensive care admission	32 (16%)	41 (20%)	0·209
Nausea, mm on a VAS§	2 (0–24)	0 (0–8)	0·007
Emesis	10 (5%)	7 (3%)	0·476
Antiemetic rescue	39 (19%)	26 (13%)	0·090
First solid food, postoperative days	4·8 (2·4)	4·8 (2·0)	0·938
Time to first flatus, days	3·5 (1·7)	3·5 (1·8)	0·917
Time to first bowel movement, days	3·8 (1·6)	3·9 (1·9)	0·533
Duration of hospital stay, days	11·1 (4·9)	11·6 (7·2)	0·387
Mortality within 15 days	0	3 (2%)	0·120

Data are mean (SD), number of patients (%), or mean (IQR). CDC=Centers for Disease Control and Prevention. *Superficial, deep, and peritoneal infections are not mutually exclusive. Infections as diagnosed by expression of culture-positive pus and by CDC criteria are not mutually exclusive. Consequently the total infection column is not the sum of each infection type. †ASEPSIS is a wound-healing score. ‡Collagen deposition was measured in only 52 patients (21 in nitrous oxide group and 31 in nitrogen group). §Measured 2 h after surgery on a visual analogue scale for nausea: 0 mm=no nausea; 100 mm=worst imaginable nausea.

Table 3: **Principal results**

	Beta	Odds ratio	95% CI	p
Gas (nitrogen *vs* nitrous oxide)	0·11	1·26	(0·66–2·34)	0·487
Age	0·99	0·99	(0·96–1·01)	0·287
Smoking (no *vs* yes)	0·69	0·69	(0·29–1·63)	0·396
Sex (female *vs* male)	0·96	0·96	(0·47–1·99)	0·920
Weight	0·02	1·02	(1·00–1·05)	0·070
ASA				
I *vs* III	−0·76	0·34	(0·07–1·64)	0·051
II *vs* III	0·44	1·13	(0·32–3·94)	0·103
SENIC				
1 *vs* 3	0·20	1·17	(0·28–4·85)	0·639
2 *vs* 3	−0·23	0·77	(0·30–1·93)	0·395
NNISS				
1 *vs* 3		0·36	(0·05–2·92)	0·184
2 *vs* 3		1·07	(0·27–4·22)	0·124
Duration of surgery	−0·04	0·97	(0·68–1·37)	0·839
Blood transfusion (yes *vs* no)	0·14	1·15	(0·91–1·45)	0·241
Intercept	−2·19			0·081

Table 4: **Multiple logistic regression results for surgical wound infection**

Nitrous oxide, unlike nitrogen, is an anaesthetic and provided about a 0·6 minimum alveolar concentration (MAC). MAC is the anaesthetic concentration that prevents movement in response to skin incision in 50% of patients and is a typical clinical dose.[25] Despite assertions to the contrary,[29] MAC fractions of inhaled anaesthetics are additive.[30] One might thus expect that isoflurane administration, which was adjusted clinically, would differ substantially in the two treatment groups. In fact, the difference was less than 0·1% isoflurane, which corresponds to less than 10% MAC. The reason, presumably, is that all patients were given an infusion of the opioid remifentanil, which reduced isoflurane requirement and therefore the differences between the groups.[31]

All general anaesthetics,[32] including isoflurane,[33] impair immune function at least to some degree. However, isoflurane may do so less than other volatile anaesthetics,[34] and immune effects have never been reported at low concentrations. Thus the tiny difference in isoflurane concentration between the groups (<10% MAC) is unlikely to have significantly confounded our results.

In the context of our findings, we suggest that nitrous oxide should not be avoided for fear of augmenting the risk of surgical wound infection.

Study investigators

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Contributors

E Fleishmann, R Lenhardt, A Kurz, and O Akça participated in the organisation of the centre Vienna General Hospital, University of Vienna, Austria; E Fleishmann was involved in patient recruitment, perioperative study organisation, data management, and manuscript preparation; R Lenhardt was involved in data management and manuscript preparation; A Kurz undertook protocol preparation and manuscript preparation; F Herbst was involved in patient recruitment, postoperative study organisation (blinded wound assessments), and manuscript preparation; B Fülesdi participated in the organisation of the centre in Debrecen, Hungary and undertook patient recruitment, organisation of data collection, and manuscript preparation; R Greif participated in the organisation of the centre SMZ-Ost Vienna, Austria, and was involved in patient recruitment, organisation of data collection, and manuscript preparation; D I Sessler was involved in protocol preparation, overall organisation of all centres, database preparation, data management, and manuscript preparation; and O Akça undertook protocol preparation, perioperative study organisation, data management, and manuscript preparation.

Conflict of interest statement

We declare that we have no conflict of interest.

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