Acta Anaesthesiol Scand 1993: 37: 683–686
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Acta Anaesthesiologica Scandinavica
ISSN 0001-5172

Peroperative nitrous oxide does not influence recovery after laparoscopic cholecystectomy

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We have evaluated the effects of nitrous oxide on recovery following laparoscopic cholecystectomy in a prospective, randomised, double-blind study with 42 otherwise healthy patients. All patients received meperidine 1 mg/kg and atropine 6 μg/kg im for premedication, and anaesthesia was induced with fentanyl 2 μg/kg and thiopental 4–6 mg/kg. Succinylcholine was used for the intubation and muscle relaxation was achieved using vecuronium. Isoflurane with 70% nitrous oxide in oxygen and fentanyl was used for maintenance of anaesthesia in group I (n = 19), and isoflurane in air/oxygen and fentanyl in group II (n = 23). The postoperative ward staff and the surgeon evaluating the postoperative recovery were blinded to the anaesthetic technique. No differences were found in duration of operation and anaesthesia, need for postoperative analgesia or postoperative nausea treated medically. Recovery, judged by the Steward Coma Score, comprehension and collaboration, degree of sedation and orientation in time and space, was similar in the two groups. Postoperative hospital stay was 1 (1–4) day in the nitrous oxide group (median (10–90th percentiles) versus 2 (1–4) days in the air group. The time until patients were recovered, as judged by return to work and normal daily activities, was the same in the two groups: 8 (4–11) days in the nitrous oxide group and 8 (4–11) days in the air group. We conclude that nitrous oxide has no influence on recovery after laparoscopic cholecystectomy.

Received 2 September, accepted for publication in a revised version 29 December 1992

Key words: Anesthesia: laparoscopic cholecystectomy; anesthetics, volatile: isoflurane; nitrous oxide; postoperative recovery.

The anaesthetic technique used for laparoscopic cholecystectomy needs to be evaluated. Many anaesthetists prefer to avoid nitrous oxide (N_2O) because bowel distension could, theoretically, obscure vision during the operation (1) and thereby prolong surgery. In addition, N_2O may be associated with a risk of more complications leading to longer hospital stay and longer postoperative recovery (1). We therefore designed this prospective, randomised, double-blind study to evaluate the effects of N_2O on recovery following laparoscopic cholecystectomy.

PATIENTS AND METHODS

The study was performed in accordance with the Helsinki II Declaration and approved by the Human Ethics Committee of the University Hospital in Linköping. Forty-two patients scheduled for laparoscopic cholecystectomy gave informed consent to participate in the study.

All patients received meperidine 1 mg/kg and atropine 6 μg/kg im for premedication approximately 45 min prior to anaesthetic induction. Anaesthesia was induced intravenously with fentanyl 2 μg/kg, and thiopental 4–6 mg/kg was administered until loss of eyelash reflex. Tracheal intubation was facilitated by the use of succinylcholine 1 mg/kg after pretreatment with vecuronium 1 mg. For maintenance of anaesthesia the patients were randomly assigned to one of two treatment groups using standardised anaesthetic techniques: patients in group I received isoflurane with N_2O in oxygen, and patients in group II received isoflurane with air in oxygen. In both groups an inspiratory fraction of oxygen of 0.3 was used. A low-flow circle system with humidified, warm gases was used for ventilation of the lungs, and normoventilation based on measurement of end-tidal carbon dioxide ($ETco_2$) was achieved. Small incremental bolus doses of vecuronium (0.5–1 mg) were administered to maintain adequate muscle relaxation, as judged by tactile evaluation of twitch after a train-of-four stimulation. The end-tidal isoflurane concentration was measured (Capnomac Ultima®, Datex) and adjusted as necessary to maintain an adequate depth of anaesthesia during the operation. Every change in concentration was noted by the anaesthetist in the journal and after completion of the trial the mean end-tidal concentration in percent per hour was calculated. Clinical signs of inadequate anaesthesia (2) were used as guidelines of stability. The concentration of isoflurane was changed at the following clinical signs (2): I: Increase in systemic arterial systolic pressure greater than 15 mmHg (2 kPa) above preoperative value. II: A heart rate exceeding 90 beats/min in the absence of hypovolaemia. III: Somatic responses including bodily movements, swallowing, coughing, grimacing or eye opening. IV: Other signs of inadequate anaesthesia such as lacrimation, flushing or sweating. An additional dose of fentanyl 1.5–2 μg/kg was given before skin incision. During the operation the patients were monitored with ECG, pulse oximetry, end-tidal carbon dioxide, end-tidal isoflurane concentration and non-invasive automatic blood pressure measurements every 5 min. During the operation carbon dioxide was insufflated into the abdomen. Isoflurane and N_2O were discontinued at the end of surgery, and residual neuromuscular block was reversed with neostigmine 2.5 mg, given together with glycopyrrolate 0.5 mg iv.

In the postoperative ward patients were monitored with ECG and by non-invasive blood pressure measurements. Recovery was assessed by a nurse, blinded to treatment allocation, who evaluated the Steward Coma Scale (3), orientation in time and space, comprehension and collaboration and degree of sedation (Table 1) at 15-min intervals. Patients were questioned for complaints of nausea and pain every 30 min during their stay.

During their stay in hospital the patients were given medical treatment for nausea and pain on request. The antiemetic drugs used were phenothiazines. After discharge the patients were followed until they could return to work or normal daily activity. The surgeon evaluating the postoperative course was blinded to the group allocation and provided the results for the final evaluation of the study after its completion.

Before statistical analysis, all quantitative data were displayed as percentile distributions to study homogeneity in each group. Differences between distributions were tested with the Mann-Whitney U-test, and the chi-square test was used for dichotomous values. Results are given in median (10–90th percentile) if not otherwise stated. The level of statistical significance was set at $P<0.05$. A statistical power analysis was performed to determine the probability of a type II (or β) error. Two parameters were studied. We wanted to be able to demonstrate a reduction of 30 min in mean operation time and a reduction of 3 days in time until recovery. We found a mean operation time in the N_2O group of 116 min, s.d 32 min, and a mean time until recovery in the N_2O group of 9.1 days, s.d. 2.8 days. A nomogram for calculating the sample size for continuous variables with a significance level of alpha = 0.05 and beta = 0.20 was used (4). This suggested that the number of patients in the two groups was adequate to support our conclusions.

Table 1

The postoperative performance scores.

Modified Steward Coma Score	Score
A Consciousness:	
Not responding	0
Responding to ear-pinching	1
Eyes open on command or in the response to name	2
Lightly asleep, eyes open intermittently	3
Fully awake/eyes open/conversing	4
B Airway:	
Obstructed without support	0
Obstructed on flexion/clear on extension of neck	1
No voluntary cough/airway clear without support	2
Opening mouth or coughing or both on command	3
C Activity:	
Not moving	0
Non-purposeful movement	1
Raising one arm on command	2
Total maximum score of A + B + C	9
Orientation in time and space:	
No response	1
Total disorientation	2
Only orientation in space is present	3
Only orientation in time is present	4
Excellent/both orientations are present	5
Comprehension and collaboration:	
No execution of the order	1
Execution of the order by imitation	2
Execution of the order	3
Degree of sedation:	
Sleeping heavily	1
Sleeping, but easily awakened	2
Awake but dull	3
Awake	4

RESULTS

Data from 40 of the 42 patients entering the study could be used for evaluation. One patient in each group had a major postoperative complication not attributable to the anaesthetic technique, and they were therefore excluded from the evaluation. The two groups were comparable with respect to age and weight (Table 2). Duration of operation and anaesthesia as well as time from discontinuation of anaesthesia until sustained breathing and extubation of the trachea did not differ between the two groups (Table 2). No differences were found in the dose requirements of thiopental, vecuronium or fentanyl (Table 3), or in the number of adjustments of isoflurane concentration. The mean end end-tidal concentration of isoflurane was higher in group II (Table 3).

All patients were haemodynamically stable during their stay in the postoperative ward, and no differences were seen in Steward Coma Score, orientation in time and space, comprehension and collaboration or degree of sedation (Table 4). Requirements for antiemetic therapy (group I 58% and group II 43% of the patients, $P=0.25$) and analgesia (group I 63% and group II 48% of the patients, $P=0.25$) during the total hospital stay were the same in the two groups. The number of doses of antiemetics per patient were 1 to 4 in group I and 1 to 6 in group II, respectively.

The indication for laparoscopic cholecystectomy was gallbladder stones, and the operations were performed electively in all but four patients, who had urgent operations because of acute cholecystitis (group I: three patients, group II: one patient). Furthermore, one patient in group I and three patients in group II were treated postoperatively with endoscopic sphincterotomy because of common bile duct stones. The patient from group I excluded from the study was operated during acute cholecystitis and had pneumonia and sepsis postoperatively, leading to a total postoperative hospital stay of 13 days, and was home for 33 days before full recovery. One patient from group II developed coronary ischaemia during operation and spent 3 days in the cardiac intensive care unit. He was discharged with a diagnosis of angina pectoris, and was excluded from the study.

The mean postoperative time in the ward was similar: 1 (1–4) day in group I and 2 (1–4) days in group

Table 2

Demographic data of the patients, anaesthesia and surgical characteristics and corresponding *P*-values. Data shown in median (10–90th percentile). No differences could be found between the groups.

	Group I (with N_2O)	Group II (without N_2O)	*P* value
Age (Y)	47 (28–71)	52 (28–70)	0.25
Weight (kg)	65 (55–83)	70 (63–92)	0.06
Duration of surgery (min)	105 (90–168)	105 (80–193)	0.8
Duration of anaesthesia (min)	165 (127–210)	165 (125–240)	0.6
Time to sustained breathing (min)	9 (3–19)	5 (0–15)	0.2
Time to tracheal extubation (min)	11 (7–24)	10 (4–25)	0.6

Table 3

Requirements of thiopental, fentanyl and vecuronium in total doses per kg body weight. End-tidal isoflurane concentration per hour and the number of adjustments of isoflurane concentration necessary. Corresponding *P* values shown, data given as median (10–90th percentiles). The concentration of isoflurane was higher in group II, otherwise there were no differences between the two groups.

	Group I (with N_2O)	Group II (without N_2O)	*P* value
Thiopental [mg/kg]	4.8 (4.0–0.7)	4.0 (3.5–5.7)	0.07
Fentanyl [μg/kg]	5.5 (3.5–7.7)	5.6 (3.7–7.2)	0.12
Vecuronium [mg/kg]	0.13 (0.06–0.16)	0.12 (0.08–0.17)	0.9
End-tidal isoflurane [%/h]	0.7 (0.55–0.92)	1.1 (0.8–1.32)	0.01
Number of adjustments	7 (3–10)	7 (4–10)	0.9

II, and time until recovery or to normal daily activity was also similar: 8 (4–11) days in group I and 8 (4–11) days in group II. No statistically differences between the two groups could be demonstrated (Fig. 1).

Table 4

The result of postoperative observation of recovery and the corresponding *P* values. Data are shown as mean ± s.d. There were no differences between the two groups.

	Group I (with N_2O)	Group II (without N_2O)	*P* value
Steward Coma Score			
30 min after extubation	7.8 ± 0.8	7.7 ± 1.0	0.9
60 min after extubation	8.2 ± 0.8	8.3 ± 1.0	0.5
90 min after extubation	8.5 ± 0.5	8.6 ± 0.6	0.7
120 min after extubation	8.7 ± 0.5	8.8 ± 0.4	0.6
Orientation in time and space			
30 min after extubation	4.3 ± 1.0	4.1 ± 1.1	0.7
60 min after extubation	4.6 ± 0.8	4.6 ± 0.9	0.8
90 min after extubation	4.8 ± 0.6	4.9 ± 0.5	0.8
120 min after extubation	4.8 ± 0.6	4.9 ± 0.4	0.4
Comprehension and collaboration			
30 min after extubation	2.9 ± 0.2	2.8 ± 0.5	0.6
60 min after extubation	3.0	3.0	1
90 min after extubation	3.0	3.0	1
120 min after extubation	3.0	3.0	1
Degree of sedation			
30 min after extubation	3.1 ± 0.7	2.7 ± 0.8	0.1
60 min after extubation	3.2 ± 0.8	3.2 ± 0.9	0.9
90 min after extubation	3.4 ± 0.9	3.4 ± 0.8	0.8
120 min after extubation	3.5 ± 0.8	3.5 ± 0.8	0.9

DISCUSSION

The major findings in this study were the lack of influence of N_2O on postoperative emesis and recovery following laparoscopic cholecystectomy. N_2O is used as an analgesic and anaesthetic adjuvant to general anaesthesia, but, due to its high solubility, it can diffuse from blood into air-containing closed body cavities and cause distension of the bowel (5). Clinical studies have demonstrated that N_2O can produce bowel distension during surgery (1). These operations were, however, longer than the procedures in our study, and longer surgical procedures will produce a more complete equilibration between bowel gas and the N_2O

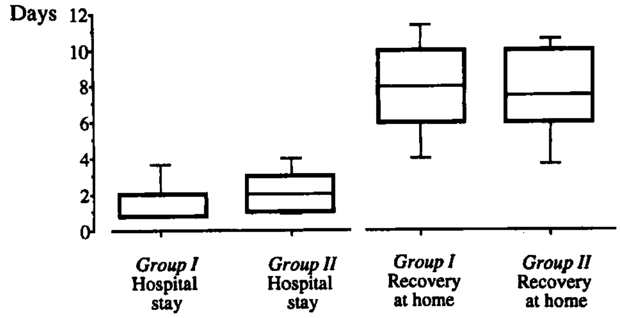

Fig. 1. Days spent in hospital and at home until recovery. There were no differences between groups I and II. Data are shown as median and percentiles, boxes representing the 25th to 75th and end lines the 10th to 90th percentiles.

in the inspired gas (5), resulting in a greater increase in bowel volume. Another difference was that they (1) injected 200 ml air through a tube placed in the stomach at the start of the operation as a "seed volume". Since the average gas content in the intestine is approximately 100 ml (6), this injected air probably contributed to the bowel distension, which may be further expanded by N_2O diffusing into the bowel.

This study design did not allow us to evaluate peroperative bowel distension, but we think that if this had been substantial the effects would also have been obvious in the postoperative parameters measured in this study. In a recent study by Taylor et al. (7), no difference in bowel distension due to N_2O could be demonstrated in patients undergoing laparoscopic cholecystectomy. Their anaesthetic technique was similar to ours and the results are in accordance with this study.

An increase in postoperative emetic sequelae was previously reported to be attributable to N_2O (8), or unaffected by N_2O (9). A high incidence of nausea was confirmed in our study, but in contrast to previous studies (8) there were no differences associated with the use of N_2O. This suggests that the cause of the nausea is attributable to the surgery, rather than the anaesthetic technique.

Insufflation of the abdominal cavity with carbon dioxide (CO_2) may lead to ventilatory complications such as pulmonary atelectasis, decreased functional residual capacity, and high airway pressure (10), and circulatory complications due to increased intraabdominal pressure resulting in decreased venous return and hypotension (11). Further, the risk of venous CO_2 embolism (12) must be considered. End-tidal monitoring of CO_2 is essential to register whether absorption of CO_2 causes hypercarbia, and whether CO_2 embolism occurs (13). Most reports of complications following intraabdominal insufflation of CO_2 have been based on gynaecological operations, which are usually shorter than laparoscopic cholecystectomy. The risk of complications of CO_2 absorption may increase as laparoscopic procedures become longer. Regarding inhalational anaesthetics, isoflurane is theoretically appropriate to use in these settings since the risk of cardiac arrhythmia from increased arterial partial pressure of CO_2 is low (14).

Concerns about pollution with N_2O anaesthesia (15) may prevent unnecessary use of this gas during anaesthesia. However, since N_2O possesses useful properties, other efforts to avoid pollution, such as low-flow anaesthesia and prevention of unnecessary gas leaks, should be considered instead of completely avoiding N_2O. In conclusion, this study suggests that the intra- and postoperative course after laparoscopic cholecystectomy is not adversely affected by the use of N_2O.

ACKNOWLEDGEMENTS

The authors thank the nurses and staff of the anaesthetic department, postoperative ward and surgical ward 5, University Hospital in Linköping for their valuable assistance.

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