

## Supplemental oxygen does not reduce postoperative nausea and vomiting after thyroidectomy<sup>†</sup>

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**Background.** Supplemental intra-operative oxygen 80% halves the incidence of nausea and vomiting after open and laparoscopic abdominal surgery, perhaps by ameliorating intestinal ischaemia associated with abdominal surgery. It is unlikely that thyroid surgery compromises intestinal perfusion. We therefore tested the hypothesis that supplemental perioperative oxygen does not reduce the risk of postoperative nausea and vomiting (PONV) after thyroidectomy.

**Methods.** One hundred and fifty patients undergoing thyroidectomy were given sevoflurane anaesthesia. After induction, patients were randomly assigned to the following treatments: (i) 30% oxygen, (ii) 80% oxygen, or (iii) 30% oxygen with droperidol 0.625 mg.

**Results.** The overall incidence of nausea during the first 24 h after surgery was 48% in the patients given oxygen 30%, 46% in those given oxygen 80%, and 22% in those given droperidol ( $P=0.004$ ). There were no significant differences between the oxygen 30% and 80% groups in incidence or severity of PONV, the need for rescue antiemetics, or patient satisfaction. Droperidol significantly shortened the time to first meal.

**Conclusions.** Supplemental oxygen was ineffective in preventing nausea and vomiting after thyroidectomy, but droperidol reduced the incidence.

*Br J Anaesth* 2003; **91**: 857–61

**Keywords:** complications, postoperative; hypnotics butyrophenone, droperidol; oxygen, perioperative; surgery, thyroidectomy; vomiting, nausea

Accepted for publication: June 6, 2003

Postoperative nausea and vomiting (PONV) is one of the problems most feared by surgical patients.<sup>1</sup> Uncontrolled PONV remains the leading cause of delayed discharge or unexpected admission after ambulatory surgery.<sup>2</sup> The incidence of PONV varies widely and depends on numerous non-anaesthetic and anaesthesia-related factors.<sup>3–5</sup> However, the risk is substantial in most populations.

The incidence of PONV after open colectomy is halved in patients receiving oxygen 80% perioperatively compared with those receiving 30%.<sup>6</sup> Supplemental oxygen has also been shown to halve the risk after laparoscopic gynaecological surgery in one study,<sup>7</sup> whereas another found no benefit.<sup>8</sup> The mechanism by which supplemental oxygen reduces PONV remains unknown, but may be related to

hyperoxia ameliorating subtle intestinal ischaemia secondary to bowel manipulation and/or compression. Any reduction in bowel ischaemia would presumably decrease release of emetogenic substances,<sup>7,9</sup> and therefore, the risk of PONV.

The risk of PONV varies widely as a function of the surgical procedure. For example, PONV is common after thyroid surgery.<sup>3,10,11</sup> The specific aetiology remains unknown, but is probably not related to perioperative intestinal ischaemia. We therefore tested the hypothesis that supplemental perioperative oxygen does not reduce the risk

<sup>†</sup>Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, October 13–17, 2001.

of PONV after thyroidectomy. As a positive control, we simultaneously evaluated the efficacy of droperidol 0.625 mg.

## Methods

With approval from the institutional ethics committee at CHU de Liège and written informed consent, 150 patients scheduled for elective thyroid surgery were included in this prospective, double blind study. Enrolment was restricted to patients aged 19–70 yr who were ASA status I–III. Exclusion criteria included obesity (>150% ideal body weight), gastro-oesophageal reflux, history of motion sickness, previous PONV, preoperative vomiting, antiemetic therapy, and any pulmonary disease.

Patients were informed before surgery that pharmacological treatment for nausea and vomiting would be available upon request after surgery. Patients were given alprazolam 0.5 mg and hydroxyzine 25 mg orally 1 h before transfer to the operating theatre. Anaesthesia was induced with propofol 2 mg kg<sup>-1</sup>, sufentanil 0.2 µg kg<sup>-1</sup>, and rocuronium 0.6 mg kg<sup>-1</sup>. Anaesthesia was subsequently maintained with sevoflurane at a concentration that was adjusted to maintain arterial blood pressure within 20% of pre-induction values.

After induction of anaesthesia, patients were randomly assigned to the following three groups: (i) routine oxygen administration with oxygen 30% (*n*=50); (ii) supplemental oxygen administration with oxygen 80% (*n*=50); and (iii) droperidol 0.625 mg immediately after induction of anaesthesia, combined with oxygen 30% (*n*=50). Patients and surgeons were blinded as to group assignment.

Crystalloid was given at a rate of 8 ml kg<sup>-1</sup> h<sup>-1</sup> throughout surgery. No patients required antagonism of neuromuscular block. Inspired oxygen was increased to 100% for extubation. The patients were subsequently given oxygen at the designated concentration (30 or 80%) via face mask for 2 h at a rate of 9 litre min<sup>-1</sup>. Two hours after surgery, the face mask was removed. We used a face mask with non-rebreathing valves and a 500 ml reservoir (Trident Medical International, Copenhagen, Denmark).

Postoperative analgesia was standardized and consisted of i.v. administration of propacetamol 2 g, which is endogenously converted into acetaminophen 1 g (Pro-Dafalgan®, UPSA Medica, Belgium) and tramadol 2 mg kg<sup>-1</sup> 30 min before the end of surgery. Upon arrival in the post-anaesthetic care unit, piritramid, a synthetic opioid (Dipidolor®, Janssen Pharmaceutica, Beerse, Belgium), was titrated i.v. by post-anaesthetic care unit nurses to provide satisfactory analgesia. These nurses were blinded to group assignment.

Thirty minutes after the end of surgery, provided there was no evidence of postoperative bleeding, ketorolac 30 mg was given i.v. followed by a continuous infusion of 30 mg over 6 h. Propacetamol (2 g i.v.), acetaminophen (1 g

**Table 1** Patient data. Data presented as mean (SD or range) or number. \*Significantly different from the oxygen 80% and droperidol groups, *P*=0.006

	Oxygen 30%	Oxygen 80%	Droperidol
Age (yr)	45 (23–70)*	50 (27–70)	53 (32–69)
Weight (kg)	66 (13)	69 (14)	71 (13)
Height (cm)	165 (7)	165 (8)	165 (8)
Sex (F/M)	42/8	43/7	41/9
Smoking (Y/N)	15/35	16/34	19/31
Duration of anaesthesia (min)	116 (30)	111 (21)	122 (23)
Intraoperative sufentanil (µg)	16 (4)	16 (3)	16 (4)
Total/partial thyroidectomy	42/8	43/7	46/4
Postoperative piritramid (mg)	4 (3)	4 (2)	3 (4)
Patients given piritramid	29	24	19

orally), and tramadol (100 mg i.v. or orally) were given as rescue medications.

Nausea and vomiting were treated, upon request, with alizapride 50 mg, a dopaminergic receptor antagonist; treatment continued with tropisetron 2 mg, a selective 5-HT<sub>3</sub> receptor antagonist, if PONV persisted for >30 min. Patient characteristics were recorded. Details of anaesthesia and surgical management were recorded.

Postoperative pain scores were evaluated with 100 mm visual analogue scales 2, 6, and 24 h after surgery. Pain therapy was recorded during the first 24 h after the end of surgery. Patients were allowed to drink 4 h after surgery and, if tolerated, to eat after an additional hour. The postoperative times until the first drink and solid intake were recorded. Patient satisfaction concerning postoperative physical comfort and well-being were scored with 100 mm visual analogue scales, with 100 mm indicating complete satisfaction.

Blinded observers recorded the incidence and the severity of nausea and vomiting during the three following postoperative periods: 0–2 h, 2–6 h, and 6–24 h. Severity of nausea was assessed on a 4-point scale as none, mild, moderate, or severe. Retching was recorded as vomiting.

Continuous variables were analyzed by one-way ANOVA. The Kruskal–Wallis test was used to compare time to first drink, time to first meal, and patient satisfaction. Categorical variables were analyzed using  $\chi^2$ -test analysis. Data are presented as mean (SD), percentage, or median (10th–90th percentile). *P*<0.05 was considered statistically significant.

## Results

Patient characteristics in all groups were similar except for age; the patients in the oxygen 30% group were younger than those in the other groups. Anaesthetic and surgical management (Table 1), postoperative pain (Table 2), and analgesic consumption were also similar in the groups. Six patients in the oxygen 30% group and two in the droperidol group had oxygen saturation <95% after the operation.

**Table 2** Postoperative pain, and nausea and vomiting. Pain was scored with a 100-mm visual analogue scale. Data are presented as number (%), except for pain scores given as mean (SD). \*95% CI for the differences between the proportions in the oxygen 30% and 80% groups were -0.18 to 0.22 for nausea, -0.14 to 0.18 for vomiting, and -0.23 to 0.15 for antiemetic. \*\*Significantly different from the oxygen 30% and 80% groups,  $P=0.004$

	Oxygen 30%	Oxygen 80%	Droperidol
0–2 h after surgery			
Nausea	12 (24)	8 (16)	4 (8)
Nausea score (none/mild/moderate/severe)	38/7/2/3	42/3/4/1	46/3/0/1
Vomiting	1 (2)	3 (6)	1 (6)
Alizapride/tropisetron	7/0	9/3	3/0
Postoperative pain score (mm)	33 (22)	34 (20)	32 (21)
2–6 h after surgery			
Nausea	15 (30)	15 (30)	7 (14)
Nausea score (none/mild/moderate/severe)	35/8/3/4	35/9/5/1	43/3/1/3
Vomiting	6 (12)	6 (12)	3 (6)
Alizapride/tropisetron	8/3	7/0	6/1
Postoperative pain score (mm)	23 (20)	21 (20)	21 (22)
6–24 h after surgery			
Nausea	9 (18)	8 (16)	5 (10)
Nausea score (none/mild/moderate/severe)	41/6/1/2	42/6/0/2	45/1/3/1
Vomiting	6 (12)	2 (4)	3 (6)
Alizapride/tropisetron	3/0	3/2	2/2
Postoperative pain score (mm)	15 (14)	15 (14)	13 (16)
0–24 h after surgery*			
Nausea	24 (48)	23 (46)	11 (22)**
Vomiting	12 (24)	11 (22)	6 (12)
Antiemetic	19 (38)	21 (42)	12 (24)

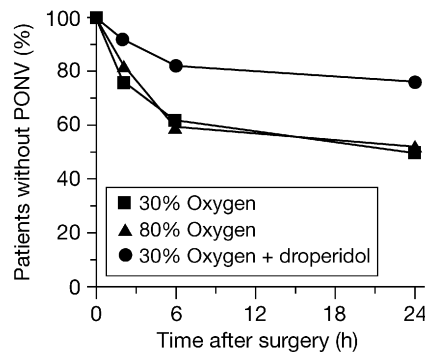
These patients were stimulated and encouraged to breath deeply. SpO<sub>2</sub> increased spontaneously above 95% without giving oxygen supplement.

When the entire 24 h observation period was considered, droperidol halved the incidence of nausea compared with the two other groups (Table 2,  $P=0.004$ ). The incidence of nausea and vomiting in the oxygen 30% and 80% groups did not differ significantly (Fig. 1). For the 0–24 h time period the incidences of nausea were 0.48 and 0.46 (95% CI for the difference between proportions was -0.18 to 0.22) and the incidences of vomiting were 0.24 and 0.22 (95% CI for the difference between proportions was -0.14 to 0.18) for the oxygen 30% and 80% groups, respectively. This study achieved a 90% power to detect a 50% reduction in the rate of PONV between the oxygen 30% and the oxygen 80% group at an alpha level of 0.05.

In the droperidol group, time to the first meal was significantly shorter than in the oxygen 30% and 80% groups. Patient satisfaction was comparable in all groups (Table 3). Patient satisfaction was significantly greater in patients with no PONV as compared with patients with PONV: visual analogue scale scores of 91 (70–100) vs 80 (44–98),  $P<0.006$ .

### Discussion

This study failed to observe any benefit of supplemental oxygen on PONV after thyroidectomy and confirmed the antiemetic efficacy of droperidol. Gut manipulation during colon surgery and the associated splanchnic vessel dissection probably results in at least some intestinal ischaemia.<sup>12</sup> Indeed, the stress of major surgery *per se* stimulates the



**Fig 1** Percentage of patients who did not experience PONV. Patients were given oxygen 30%, oxygen 80%, or oxygen 30% combined with droperidol. Patients given droperidol experienced significantly less nausea and vomiting than patients given either other treatment.

sympathetic nervous system and can substantially reduce splanchnic blood flow. Even slight intestinal ischaemia triggers substantial release of 5-hydroxytryptamine and other emetogenic factors.<sup>13</sup> Supplemental perioperative oxygen presumably reduces the amount of ischaemic intestinal tissue and thus, the risk of nausea and vomiting.

Pneumoperitoneum, which is required for laparoscopic procedures, also induces significant haemodynamic changes and release of vasoactive hormones<sup>14 15</sup> that can reduce intestinal perfusion.<sup>15–17</sup> However, the extent to which laparoscopy impairs intestinal perfusion may depend on subtle details of surgical technique—perhaps explaining why supplemental oxygen was beneficial in one study of laparoscopic gynaecological surgery,<sup>7</sup> but not in another.<sup>8</sup>

Thyroid surgery differs from abdominal surgery in that intestinal ischaemia is unlikely because the surgical

**Table 3** Time to first drink, time to first meal, and patient satisfaction. Patient satisfaction was scored using a 100-mm visual analogue scale. Data are presented as median (10th–90th percentiles), and analysed using the Kruskal–Wallis test. \*Significantly different from the oxygen 30% and 80% groups,  $P=0.02$

	Oxygen 30%	Oxygen 80%	Droperidol
First drink (h)	4.0 (3.7–7.0)	4.2 (3.6–6.0)	4.4 (4.0–5.7)
First meal (h)	6.6 (4.3–15.5)	7.0 (5.2–15.3)	5.8 (4.5–9.7)*
Patient satisfaction (mm)	84 (56–100)	85 (53–100)	91 (56–100)

procedure does not directly involve the splanchnic circulation. Furthermore, the risk of significant bleeding is low. Hypotension, and consequent intestinal hypoperfusion, is thus rare during thyroid surgery. That supplemental oxygen did not reduce the risk of nausea and vomiting is consistent with the theory that oxygen prevents PONV by ameliorating subtle intestinal ischaemia rather than by acting directly at the chemotactic trigger zone.

The difficulty with this theory is a recent study in which prophylactic supplemental oxygen was found to reduce the incidence of nausea and vomiting in victims of minor trauma who developed motion sickness during ambulance transport.<sup>18</sup> It is unlikely that these patients had intestinal ischaemia, suggesting that the benefits of supplemental oxygen were mediated by another mechanism. The most likely is that reduction of nausea by oxygen depends on dopamine release from the carotid bodies. The carotid bodies tonically release dopamine in amounts that are inversely related to arterial oxygen tension.<sup>19</sup> The importance of this observation is that the chemotactic trigger zone is sensitive to dopamine as well as serotonin.<sup>20</sup> Hyperoxia *per se* may thus reduce nausea and vomiting via a dopamine-dependent mechanism.

That then leaves the question of why oxygen proved ineffective in patients recovering from thyroid surgery. The most likely explanation is that nausea and vomiting in these patients was mediated by yet another mechanism. There are several possibilities. For example, intraoperative dissection of the recurrent laryngeal nerve(s) may contribute because this nerve is a branch of the vagal nerve that is highly involved in emetic reflexes. PONV after thyroidectomy may also result from nociceptive reflexes originating from the pharynx and larynx.<sup>3</sup> (Pharyngeal pain, exacerbated by swallowing, is typical after thyroid surgery.) To the extent that PONV results from throat pain, it is unlikely to be affected by hyperoxia. Consistent with this theory, pain scores and analgesic consumption was similar in each of our three treatment groups. PONV has numerous aetiologies and many factors are known to influence the incidence of this complication. It is therefore unsurprising that a treatment effective for some aetiologies would fail in other circumstances.

We found that droperidol significantly reduced the incidence of PONV. This study thus confirms that

droperidol prevents PONV.<sup>21–23</sup> For example, low-dose droperidol 0.625 mg compares favourably with ondansetron 4 mg<sup>22,23</sup>—although droperidol is considerably less expensive than the 5-HT<sub>3</sub> antagonists. The incidence of side-effects are reportedly similar with each class of drugs.<sup>24–26</sup> These data suggested that the least expensive was probably preferable for routine use. However, the Food and Drug Administration has recently added a ‘black box’ warning to the label for droperidol because the drug has been associated with life-threatening QT prolongation. However, there is considerable question in the anaesthesia community about the justification for this warning.<sup>27</sup>

Patients were allowed to drink 4 h after surgery, and most did at that time or shortly thereafter. However, emetic episodes were triggered by drinking water in the oxygen 30% and 80% groups. This then delayed their first meal. As a result, droperidol not only reduced the risk of PONV, but also allowed patients to tolerate solid food significantly more quickly.

## Acknowledgements

Supported in part by NIH Grants GM 58273 and GM 061655 (Bethesda, MD, USA) and the Commonwealth of Kentucky Research Challenge Trust Fund (Louisville, KY, USA). None of the authors has any personal financial interest related to this research.

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