Can J Anesth/J Can Anesth (2020) 67:550–559
https://doi.org/10.1007/s12630-020-01584-w

REPORTS OF ORIGINAL INVESTIGATIONS

Postoperative hunger after outpatient surgery in patients anesthetized with propofol *vs* sevoflurane: a randomized-controlled trial

Faim postopératoire après une chirurgie ambulatoire chez les patientes anesthésiés à l'aide de propofol *vs* sévoflurane: une étude randomisée contrôlée

Emmanuel Besnier, MD · Anne Perdrix, MD, PhD · André Gillibert, MD · Jean Selim, MD · Benoit Froëmer, MD · Antoine Ghemired, MD · Benoit Berby, MD · Nathalie Rives, MD, PhD · Bertrand Dureuil, MD, PhD · Thomas Clavier, MD · Vincent Compère, MD, PhD

Received: 26 May 2019 / Revised: 6 November 2019 / Accepted: 21 November 2019 / Published online: 29 January 2020

Abstract

Purpose *Previous preclinical and preliminary clinical data suggest an appetite-stimulating effect of propofol compared with halogenated drugs. This study compared the effects of propofol with those of sevoflurane on recovery of hunger during the postoperative period.*

Methods *Patients undergoing outpatient transvaginal oocyte retrieval were randomized to propofol-remifentanil (propofol group) or sevoflurane-remifentanil (sevoflurane group) anesthesia. The primary endpoint was the time before feeling hungry (≥ 50/100 mm on a visual analogue scale). Secondary endpoints included plasma levels of ghrelin, leptin, and insulin (ten minutes, one hour, and two hours after anesthesia), caloric intake at first feed, and discharge readiness time.*

Results *In the 58 patients allocated to either the propofol or sevoflurane group, there was no difference in the median [interquartile range] recovery time of hunger (97 [75–138] vs 97 [80–140] min, respectively; median difference, 1; 95% confidence interval [CI], − 15 to 14; P = 0.91); caloric intake (245 [200–343] vs 260 [171–314] kcal; P = 0.39); or discharge readiness time (125 [85–153] vs 125*

Presentation: Preliminary data for this study were presented as a poster at the Congress of the French Society of Anesthesiology, 27–29 Sept 2018, Paris.

E. Besnier, MD (✉) · J. Selim, MD · T. Clavier, MD
Department of Anesthesiology and Critical Care, Rouen University Hospital, 1 rue de Germont, 76031 Rouen Cedex, France
e-mail: Emmanuel.besnier@chu-rouen.fr

Normandie University, UNIROUEN, INSERM, Rouen U1096, France

A. Perdrix, MD, PhD
Department of Biopathology, Clinical Laboratory, Henri Becquerel Centre, Rouen, France

A. Gillibert, MD
Department of Biostatistics, Rouen University Hospital, Rouen, France

B. Froëmer, MD · A. Ghemired, MD · B. Dureuil, MD, PhD
Department of Anesthesiology and Critical Care, Rouen University Hospital, 1 rue de Germont, 76031 Rouen Cedex, France

B. Berby, MD · N. Rives, MD, PhD
Gametogénèse et Qualité du Gamète, Rouen University Hospital, Rouen, France

Laboratoire de Biologie de la Reproduction-CECOS, Rouen University Hospital, Rouen, France

V. Compère, MD, PhD
Department of Anesthesiology and Critical Care, Rouen University Hospital, 1 rue de Germont, 76031 Rouen Cedex, France

Normandie University, UNIROUEN, INSERM, Rouen U1239, France

[95–174] min, P = 0.29). The groups showed no difference in crude plasma levels of ghrelin, leptin, and insulin at any time-point. When peptide plasma levels were expressed as a % change from baseline, there was a higher insulin plasma level one hour after anesthesia in the sevoflurane group (median difference, 4.9%; 95% CI, − 16.2 to 43.4) compared with the propofol group (median difference, − 21.2%; 95% CI, − 35.7 to 9.1; adjusted P = 0.01).

Conclusion *Propofol did not accelerate the recovery of hunger compared with sevoflurane after outpatient minor surgery. Moreover, propofol did not have distinguishable effects on other clinical or biological parameters associated with food intake.*

Trial registration *www.ClinicalTrials.gov (NCT02272166); registered 22 October, 2014.*

Résumé

Objectif *Des données précliniques et cliniques préliminaires suggèrent un effet de stimulation de l'appétit du propofol par rapport aux gaz halogénés. Cette étude a comparé les effets du propofol à ceux du sévoflurane sur le rétablissement de la faim en période postopératoire.*

Méthode *Des patientes subissant un prélèvement des ovocytes par voie transvaginale ont été randomisées à recevoir une anesthésie à base de propofol et rémifentanil (groupe propofol) ou de sévoflurane et rémifentanil (groupe sévoflurane). Le critère d'évaluation principal était la période de temps avant de ressentir de la faim (≥ 50/100 mm sur une échelle visuelle analogique). Les critères d'évaluation secondaires comprenaient les taux plasmatiques de ghréline, de leptine et d'insuline (à dix minutes, une heure et deux heures après l'anesthésie), l'apport calorique lors du premier repas, et le moment où les patientes étaient prêtes à recevoir leur congé.*

Résultats *Chez les 58 patientes allouées aux groupes propofol ou sévoflurane, aucune différence n'a été observée dans le temps médian [écart interquartile (ÉIQ)] jusqu'à retour de la faim (97 [75–138] vs 97 [80–140] min, respectivement; différence médiane, 1; intervalle de confiance [IC] 95 %, − 15 à 14; P = 0,91), ni dans l'apport calorique (245 [200–343] vs 260 [171–314] kcal; P = 0,39) ou le moment où elles étaient prêtes à recevoir leur congé (125 [85-153] vs 125 [95-174] min, P = 0,29). Les groupes n'ont démontré aucune différence en matière de taux plasmatiques de ghréline, de leptine et d'insuline à quelque point dans le temps que ce soit. Lorsque les taux plasmatiques de peptides étaient exprimés en % de changement par rapport aux taux de base, on a observé un taux plasmatique plus élevé d'insuline une heure après l'anesthésie dans le groupe sévoflurane (différence médiane, 4,9 %; IC 95 %, − 16,2 à 43,4) par rapport au groupe propofol (différence médiane, − 21,2 %, IC 95 %, − 35,7 à 9,1; P ajusté = 0,01).*

Conclusion *Le propofol n'a pas accéléré le retour de la faim par rapport au sévoflurane après une chirurgie ambulatoire mineure. De plus, le propofol n'a pas démontré d'effets distinctifs sur d'autres paramètres cliniques ou biologiques associés à l'ingestion de nourriture.*

Enregistrement de l'étude *www.ClinicalTrials.gov (NCT02272166); enregistrée le 22 octobre 2014.*

Early resumption of feeding after surgery is of concern for both patients and healthcare providers and reflects that the patient is returning to normal physical and psychological functioning. The ability to eat after ambulatory surgery is one of the items of the Post-Anesthetic Discharge Scoring System (PADSS) score.[1] Importantly, resumption of feeding may be a treatment in itself. For example, early feeding after major colorectal surgery reduces postoperative infection complications and shortens the time to resumed gastro-intestinal transit.[2-4] Early postoperative feeding could also be clinically important in situations of acute (e.g., cancer, inflammation) or chronic (e.g., anorexia nervosa) under-nutrition.

The sensation of hunger is finely regulated, involving both neural and peripheral mechanisms. The rise in plasma levels of ghrelin, produced by the stomach, increases hunger,[5] while insulin, produced by the pancreas, and leptin, produced by adipocytes, reduce this sensation.[6] These peptides in turn modulate the hypothalamic control of feeding behaviour.[7] The inflammatory response mediated by surgery can affect hypothalamic activity responsible for postoperative anorexia.[8]

Anesthetic drugs may alter feeding behaviour and preclinical data suggest that propofol may be orexigenic. For example, we previously reported that, unlike isoflurane, propofol induces feeding behaviour in mice for at least six hours.[9] In clinical studies, compared with isoflurane or halothane, propofol has been reported to enhance a return of the patient's appetite after neurosurgery[10] and ophthalmological procedures.[11] While it has been claimed that propofol is associated with an intense feeling of hunger in outpatients undergoing colonoscopy, no corroborating data were provided.[12]

To further our understanding of the influence of anesthetics on postoperative appetite, we compared the effects of propofol with sevoflurane on appetite and plasma levels of peptides involved in food intake. To limit potentially confounding variables related to age, sex, duration of anesthesia, and surgical procedure that may influence

postoperative hunger, we focused on a reasonably narrow patient population undergoing a standardized surgical procedure: transvaginal ultrasound-guided oocyte retrieval.

Methods

Trial characteristics

This study was approved by the ethics committee of Rouen University Hospital, France (Institutional Review Board no. 01/013/2014, 22 September, 2014) and by the French national agency for drugs and health products (*Agence Nationale de Sécurité des Médicaments et des Produits de Santé,* no. 140854A-31). The trial was registered prior to patient enrolment at clinicaltrials.gov (NCT02272166). The manuscript is written in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines. Written informed consent was obtained from all participants.

Population

Study subjects (recruited February 2015–July 2016) were adult (18–45 yr old) females undergoing scheduled oocyte retrieval under general anesthesia. All patients had undergone similar ovarian stimulation using gonadotropins, combined with either an agonist or an antagonist of the gonadotropin releasing hormone (GnRH). Exclusion criteria were American Society of Anesthesiologists (ASA) physical status score $\geq$ III, Apfel score for postoperative nausea/vomiting[13] $\geq$ 2, diabetes mellitus, cognitive impairment, body mass index (BMI) $>$ 35 $kg{\cdot}m^{-2}$, diminished nutritional status or chronic eating disorder, or chronic treatment with benzodiazepines or serotonin reuptake inhibitors. Patients anesthetized after 10:00 a.m. were excluded because of possible confounding related to prolonged fasting.

Endpoints

The primary endpoint was the time between the end of anesthesia (EOA), defined as the interruption in anesthetic administration (hypnotic and remifentanil), and the recovery of hunger, defined as $\geq$ 50/100 mm on a visual analogue scale (VAS).[14,15] Secondary endpoints included the time between EOA and ingestion of food, caloric intake at first feeding, incidence of nausea or vomiting, time for readiness to discharge from the post-anesthesia care unit (PACU), a postanesthetic discharge scoring system [PADSS] score $\geq$ 9/10[1] (see the Appendix), and plasma levels of ghrelin, leptin, and insulin at ten minutes, one, and two hours after EOA.

Study design

We conducted a randomized, 1:1 parallel-arm, prospective, patient-blinded, single-centre study comparing the effects of propofol *vs* sevoflurane on postoperative recovery of hunger. Randomization was performed using CSOnline Software v7.5.30 (Clinsight©, Poitiers, France). A single permuted block randomization list was generated with nine blocks of 12 subjects and one block of eight subjects.

Procedures were performed between 08:00 and 10:00 a.m. During the preoperative period, fasting (six hours for solids, two hours for clear liquids) was required and paracetamol 1 g was administered orally before the start of anesthesia. Hydroxyzine 0.5 $mg{\cdot}kg^{-1}$ was administered if patients were severely anxious. No preoperative administration of carbohydrates was provided. A catheter inserted in an upper extremity vein was used for administration of anesthesia drugs while a second catheter in a contralateral arm vein was used for blood sampling. Standard monitors were applied (electrocardiogram, pulse oximetry, and non-invasive blood pressure) and end-tidal expiratory gases were measured via the anesthesia machine (Zeus® and Infinity® acute care system, Drägerwerk AG, Lübeck, Germany). Patients were pre-oxygenated with 100% O_2 to achieve an expired fraction $\geq$ 90%. Remifentanil was administered with a target-controlled infusion (TCI, Minto model) of 4 $ng{\cdot}mL^{-1}$ to induce anesthesia, followed by a target effect site level of 1–4 $ng{\cdot}mL^{-1}$. Intravenous dexamethasone 4 mg and droperidol 0.625 mg were administered to help prevent postoperative nausea. In the propofol group, loss of consciousness was initiated by administering propofol using a 3–8 $\mu g{\cdot}mL^{-1}$ TCI, and maintained with a TCI of 1–10 $\mu g{\cdot}mL^{-1}$. In the sevoflurane group, unconsciousness was induced by an inhaled concentration of sevofurane 6% via a tight-fitting face mask, and was maintained with an end-tidal concentration of 1–4%. The depth of anesthesia in both groups was monitored using the bispectral index (BIS quarto Sensor® and BIS monitor®, Medtronic, USA) with sevoflurane or propofol administration adjusted to achieve a BIS target of 40–60. In both groups, a supraglottic device (i-gel®, Intersurgical Ltd, Wokingham, UK) was inserted once the depth of anesthesia was sufficient (e.g., stable blood pressure and heart rate, easy bag-and-mask ventilation, easy mouth opening). No neuromuscular blocking drug was used. Mechanical ventilation was performed with a tidal volume of 7 $mL{\cdot}kg^{-1}$ and a respiratory rate (12–20 $breaths{\cdot}min^{-1}$) to achieve an end-tidal carbon dioxide of 30–40 mmHg (air/oxygen mixture of 50% fraction of inspired oxygen, and fresh gas flow was automatically adjusted by the anesthetic machine). Nitrous oxide was not used in either group. Fluid administration was standardized

to sodium chloride 0.9% at 5 $mL \cdot kg^{-1} \cdot hr^{-1}$ during the procedure. At the end of the procedure, all drug administration was terminated and patients were ventilated with high-flow 100% oxygen. Upon awakening, the supraglottic device was removed and patients were transferred to the postanesthesia care unit (PACU) and then to the ambulatory unit. During the postoperative period, tramadol (50 mg *iv*) was administrated for pain relief followed by morphine (2 mg *iv* every five minutes), as required. Nausea and/or vomiting were treated with ondansetron 4 mg *iv*.

Nurses involved in the postoperative care of the patients (PACU and ambulatory unit) were blinded to the group allocation. Nurses evaluated the sensation of hunger every 20 min using the VAS, and as soon as the score was $\geq$ 50/100 mm, they gave the patient a meal and quantified the caloric intake. Validation of the PADSS score for readiness to discharge home was also assessed by nurses every 20 min.

Plasma measurement

Plasma levels of ghrelin, leptin, and insulin were sampled immediately before anesthesia and at ten minutes, one hour, and two hours after the EOA. At each time-point, two ethylenediaminetetraacetic acid-coated tubes were filled with blood. One of the tubes contained 1 $mg \cdot mL^{-1}$ of 4-(2-aminoethyl)-benzenesulfonyl fluoride hydrochloride to limit the *ex-vivo* degradation of ghrelin. After 15-min of centrifugation (3000 G, 4°C), the supernatant was collected and immediately frozen at − 20°C until assayed. Enzyme-linked immunosorbent assay kits were used for leptin and ghrelin analysis using duplicate measurements (ghrelin EZGRT-89K and leptin EZHL-80SK, EMD Millipore, Burlington, MA, USA). Insulin plasma levels were assessed using electrochemiluminescent immunoassay (Elecsys Insulin, Roche Diagnostics, Indianapolis, IN, USA).

Statistical analysis

All analyses were performed as intention-to-treat. Missing quantitative data were simply imputed to the median value of the other group (tendency to favour the null hypothesis). Quantitative data are presented as median [interquartile range (IQR)] and compared using a two-sided Mann–Whitney test. Qualitative data were compared with Fisher's exact test. A $P < 0.05$ was considered significant. Eighteen Mann–Whitney tests were performed to compare sevoflurane and propofol groups and the three peptides at three time-points (EOA + ten minutes, EOA + one hour, EOA + two hours) with two methods (crude values and values expressed as % in change, the latter being a *post hoc* analysis), so we adjusted the *P* value to the number of comparisons using the family-wise error rate controlling procedure following the single-step resampling method.[16] Within-groups variations of peptide levels over time were also tested by Wilcoxon paired samples tests (36 tests for three peptides, three times, two groups, and crude *vs* %-change analyses) with the same Westfall and Young procedure[16] but in a different multiple-testing family since they were unrelated. Since the treatment (sevoflurane *vs* propofol) was randomized, the baseline values were not statistically compared because we assumed that they were not different. The Hodges–Lehmann estimator was used to calculate two-sided 95% confidence intervals (CI) of differences between groups; it can be interpreted as the median of differences that would be obtained by randomly sampling a patient in each group. The primary analysis was the comparison of the time between EOA and the recovery of hunger between the two groups using a Mann–Whitney test. This test compares the area under a receiver operating curve (AUC) of the quantitative variable (time for recovery of hunger) with the binary variable (group) to the value of 0.50 (no association).

The sample size was calculated assuming an AUC equal to 0.65 (moderate association), a 1:1 randomization, power equal to 80%, a 5% type-I error rate and a two-sided formulation. Assuming a loss of power equivalent to 5% of patients (three patients per group) due to imputation of missing data, the required sample size was determined to be 58 subjects per group. Analyses were performed using SAS® (version 9.4, SAS Institute, Cary, NC, USA) and R statistical software (version 3.5.0, The R Foundation for Statistical Computing, Austria).

Results

Of the 438 screened patients, 116 were enrolled in the study, with 58 patients allocated to each group (Fig. 1). Two patients in each group did not reach the primary endpoint of recovery of hunger ($\geq$ 50/100 mm VAS). According to the intention-to-treat methodology, the median values of the other group were attributed to these patients and so data from 58 patients were analyzed. Patients in each group could not be differentiated based on age, BMI, American Society of Anesthesiology (ASA) physical status score, duration of fasting, baseline cardiorespiratory values, and Apfel score (Table 1).

The median [IQR] times between the EOA and recovery of appetite (hunger) were similar in the propofol *vs* sevoflurane groups (97 [75–138] *vs* 97 [80-–140] min, respectively; median difference, 1; 95% CI, − 15 to 14; *P*

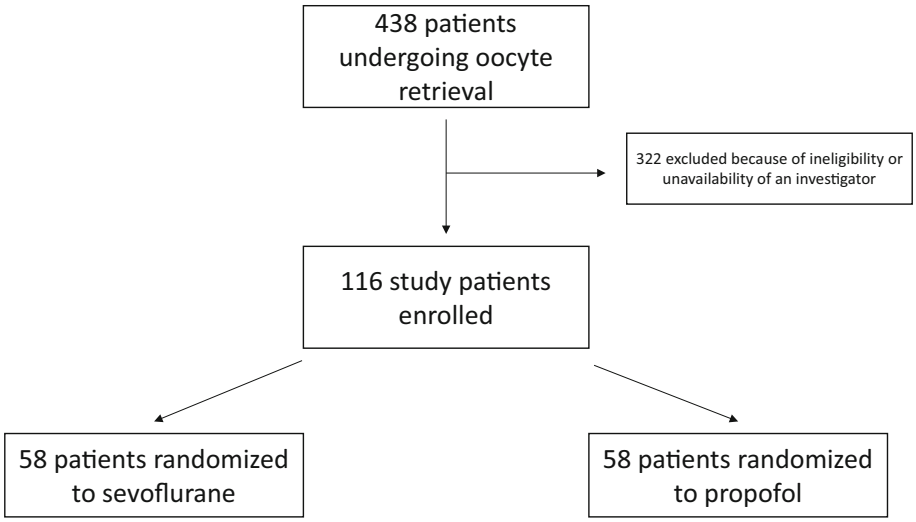

Fig. 1 Study flowchart.

Table 1 Preoperative characteristics

	Sevoflurane (n = 58)	Propofol (n = 58)
Age (yr)	32 [29–34]	33 [29–36]
Body mass index (kg·m^{-2})	22.8 [21.3–26.6]	24.8 [20.8–26.8]
ASA physical status score (n, I/II)	51/7	52/6
Preoperative hydroxyzine, n (%)	42 (72%)	41 (71%)
Preoperative solid fasting (min)	706 [670–744]	704 [665–767]
Preoperative liquid fasting (min)	630 [560–690]	619 [561–675]
Mean arterial pressure (mmHg)	70 [63–78]	70 [67–78]
Heart rate (beats·min^{-1})	60 [60–70]	60 [60–70]
Pulse oximetry (%)	99 [99–99]	99 [99–100]
Apfel score[13]	2 [2–2]	2 [1–2]

Data are presented as median [interquartile range].

ASA = American Society of Anesthesiologists; IQR = interquartile range.

= 0.91) (Table 2, Fig. 2). Similarly, the time before the first meal was not different between groups and there was no difference in the caloric intake (Table 2).

Patients in either group could not be differentiated based on readiness for discharge from the PACU or length of stay in the PACU (Table 2). A similar number of patients in either group required postoperative analgesics (Table 2). While there was no statistical difference in the occurrence of nausea and vomiting (Table 2), it is noteworthy that no patients in the propofol group experienced this compared with four in the sevoflurane group. Moreover, two patients in the sevoflurane group required anti-nausea medication in the PACU (Table 2) and one of these patients required a 24-hr hospital stay because of prolonged nausea and dizziness.

There was no difference in crude insulin, leptin, or ghrelin plasma levels (planned analysis) between groups at the three blood sampling time-points. When peptide plasma levels were expressed as a % change from baseline (*post hoc* analysis), there was a higher insulin plasma level one hour after EOA in the sevoflurane group (median difference, 4.9%; 95% CI, − 16.2 to 43.4) compared with the propofol group (median difference, − 21.2%; 95% CI, − 35.7 to 9.1), adjusted P = 0.01 (Table 3). Within each group, compared with baseline, both crude and relative insulin plasma levels were raised two hours after EOA, ghrelin levels were reduced at ten minutes, one hour, and two hours after EOA, and leptin levels were reduced at one hour and two hours after EOA (Table 3).

Patients in the sevoflurane group experienced a slightly longer median [IQR] duration of anesthesia compared with the propofol group (27 [21–30] *vs* 23 [18–29] min, respectively; P = 0.04, *post hoc* analysis) and a higher median [IQR] dose of remifentanil (3.8 [3.1–5.1] *vs* 3.5 [2.7–4.2] ng·kg^{-1}, respectively; P = 0.02, Table 2).

Table 2 Intra- and postoperative results

	Sevoflurane (n = 58) median [IQR]	Propofol (n = 58) median [IQR]	Difference (95% CI)	P
Time before feeling of hunger ≥ 50/100 mm VAS (min)	97 [80–140]	97 [75–138]	1 (− 15 to 14)	0.91
Time before meal ingestion (min)	140 [80–140]	113 [80–143]	− 3 (− 18 to 12)	0.61
Postoperative food intake (kcal)	260 [171–314]	245 [200–343]	20.5 (− 22 to 62)	0.39
Time before PADSS score ≥ 9/10 (min)	125 [95–174]	125 [85–153]	− 9 (− 26 to 8)	0.29
Stay in post-anesthesia unit (min)	76 [68–85]	75.5 [65–86]	0 (− 6 to 5)	0.93
Postoperative analgesia (yes/no)†				0.28
Tramadol (n)	12	7		
Morphine (n)	0	0		
Non-opioid (n)	5	4		
Postoperative nausea and/or vomiting (n)	4	0		0.12
Ondansetron for nausea and/or vomiting (n)	2	0		0.50
Duration of anesthesia (min)†	27 [21–30]	23 [18–29]	− 3.0 (− 6.0 to 0.0)	0.04
Intraoperative propofol dose ($mg \cdot kg^{-1}$)	-	5.7 [4.8–6.5]		
Intraoperative remifentanil dose ($\mu g \cdot kg^{-1}$)†	3.8 [3.1–5.1]	3.5 [2.7–4.2]	− 0.6 (− 1.1 to − 0.1)	0.02

VAS = visual analogue scale; CI = confidence interval; IQR = interquartile range; PADSS = postanesthetic discharge scoring system[1] (Appendix); †*Post hoc* test.

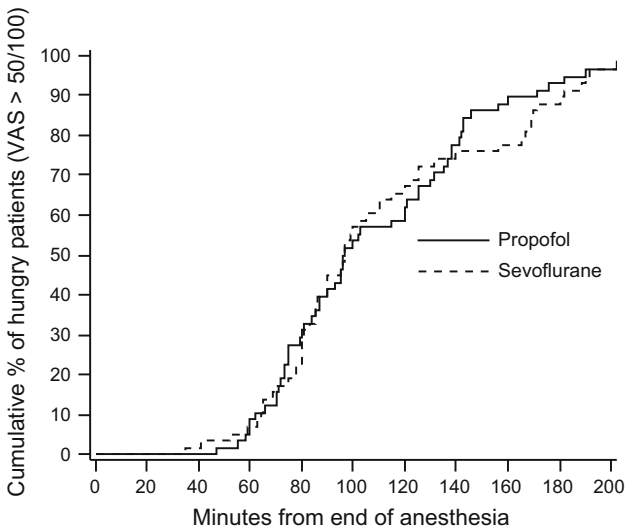

Fig. 2 Kaplan–Meier curve showing the proportion of hungry patients (VAS ≥ 50/100 mm) *vs* time (minutes from the end of anesthesia). VAS = visual analogue scale.

Discussion

We showed that the choice of hypnotic drug—propofol *vs* sevoflurane—did not influence the recovery of hunger after minor outpatient surgery. Similarly, the choice of anesthetic drug did not influence crude plasma levels of insulin, ghrelin, and leptin, all of which are related to appetite control. When plasma peptide levels were calculated as % change from baseline values, the sevoflurane group had a small increase in insulin levels at one hour following termination of anesthesia compared with the propofol group. This is the first randomized trial to specifically explore the impact of anesthetic agents on postoperative food intake. Very few studies have examined the impact of anesthesia on food intake behaviour; this is surprising given that early resumption of feeding after surgery is of major concern. Indeed, early feeding after major surgery may help to reduce postoperative complications and enhance recovery after surgery interventions.[2,17,18] Importantly, a reduced sensation of hunger and caloric intake following surgery can contribute to a catabolic state and a negative energy balance.[19] While early feeding after minor surgery may not have as great an impact, this could still influence overall patient comfort and satisfaction, facilitating an earlier return home and resumption of daily activities.

Our study design avoided several potential sources of confounding errors: type and duration of surgery, variability in inflammation, heterogeneity of patients, and variable fluid management, to name a few. Indeed, animal and human studies suggest that advanced age[20,21] or inflammation[8,22] can alter hunger and feeding behaviour. Moreover, these factors may differentially affect males and females.[8] The results of our study conflict with other findings suggesting that unlike volatile anesthetics, propofol exerts orexigenic properties.[9-12] In part, this may be explained by the different populations that have been studied as well as the type and duration of surgery.

The sensation of hunger is a complex process involving neuronal and systemic factors. The arcuate nucleus of the hypothalamus plays a key role with two specific neuronal

Table 3 Plasma levels of insulin, ghrelin, and leptin at four time-points

	Sevoflurane (n=58)	Propofol (n=58)	Difference (95% CI)	Unadjusted P value between groups	Adjusted P value† between groups
Insulin ($\mu U \cdot mL^{-1}$)					
Before anesthesia	7.9 [6.4–11.3]	7.8 [6.0–10.9]			
10 min post EOA	6.5 [4.3–10.3]	6.9 [5.1–10.0]	0.5 (− 0.9 to 2.0)	0.47	0.99
1 hr post EOA	8.4 [6.5–12.9]	7.1 [4.3–9.1]	− 2.3 (− 3.9 to − 0.6)	0.01	0.09
2 hr post EOA	15.0 [9.0–26.2]***	12.5 [5.8–25.1]**	−2.3 (− 6.3 to 1.5)	0.21	0.94
Ghrelin ($pg \cdot mL^{-1}$)					
Before anesthesia	448.4 (341.7–663.9]	448.2 [285.6–648.2]			
10 min post EOA	338.6 [247.7–463.1]***	364.2 [284.4–491.9]***	13.9 (− 49.7 to 83.9)	0.62	0.99
1 hr post EOA	336.9 [237.7–458.7]***	365.1 [279.7–523.7]***	32.4 (− 33.1 to 107.4)	0.37	0.99
2 hr post EOA	328.8 [245.7–424.6]***	319.0 [232.2–516.3]***	12.4 (− 49.0 to 88.6)	0.68	0.99
Leptin (ng/mL)					
Before anesthesia	18.2 [12.3–31.7]	18.3 [10.1–33.3]			
10 min post EOA	18.2 [12.0–29.3]	19.9 [7.6–34.4]	− 0.5 (− 6.2 to 5.1)	0.85	0.99
1 hr post EOA	17.5 [10.8–25.9]***	18.0 [7.3–27.3]***	− 1.2 (− 5.9 to 3.8)	0.67	0.99
2 hr post EOA	15.9 [9.0–27.3]***	15.5 [7.5–25.2]***	− 0.6 (− 4.6 to 4.5)	0.74	0.99
Insulin (% change *vs* baseline)					
Before anesthesia	0	0	0		
10 min post EOA	− 24.7 [− 45.9 to 18.7]	− 9.1 [− 30.1 to 17.4]	12.6 (− 2.2 to 27.9)	0.09	0.69
1 hr post EOA	4.9 [− 16.2 to 43.4]	− 21.2 [− 35.7 to 9.1]	−24.0 (− 38.1 to −10.0)	0.001	0.01
2 hr post EOA	59.6 [− 2.5 to 212.4]***	35.2 [− 9.2 to 231.2]**	−15.8 (− 53.5 to 17.7)	0.36	0.99
Ghrelin (% change *vs* baseline)					
Before anesthesia	0	0	0		
10 min post EOA	− 21.5 [− 34.3 to − 16.8]***	− 23.8 [− 32.9 to − 7.2]***	+1.5 (− 4.4 to 8.7)	0.59	0.99
1 hr post EOA	− 24.7 [− 38.6 to − 14.4]***	− 13.4 [− 29.7 to − 2.9]***	+9.9 (3.5 to 16.7)	0.004	0.06
2 hr post EOA	− 27.5 [− 43.7 to − 19.9]***	− 22.6 [− 40.1 to − 7.1]***	+5.8 (− 2.6 to 13.8)	0.18	0.99
Leptin (% change *vs* baseline)					
Before anesthesia	0	0	0		
10 min post EOA	− 8.5 [− 21.1 to 8.3]	− 8.8 [− 20.5 to 5.1]	− 0.2 (− 9.1 to 8.4)	0.96	0.99
1 hr post EOA	− 18.1 [− 25.6 to − 1.9]***	− 19.7 [− 29.1 to − 4.0]***	− 3.2 (− 9.1 to 3.6)	0.36	0.99
2 hr post EOA	− 23.9 [− 30.7 to − 14.0]***	− 21.9 [− 30.4 to − 13.4]***	1.4 (− 3.9 to 6.6)	0.63	0.99

Results are expressed as median [IQR] and were compared between groups for each peptide and each time-point by a Mann–Whitney test with a correction of P values for multiple testing. An adjusted $P < 0.05$ was considered significant. Relative change compared with baseline within each group was tested using a Wilcoxon's paired test with Bonferroni's procedure. $^{**}P < 0.01$, $^{***}P < 0.001$; all other comparisons of relative changes to baseline were non-significant ($P > 0.05$) after Bonferroni's procedure. †Adjusted for multiple-testing procedure by Westfall's method. CI = confidence interval; EOA = end of anesthesia; IQR = interquartile range.

populations: neuropeptide-Y (NPY)-producing neurons with orexigenic function[23] and pro-opiomelanocortin-producing neurons with anorexigenic function.[24] The arcuate nucleus is considered to be at the crossroads of systemic and neuronal pathways because of the particular weakness of the blood–brain barrier in this area.[23] We studied three peptides involved in feeding behaviour: ghrelin has orexigenic properties while insulin and leptin show anorexigenic properties. Insulin is secreted from β-cells in the pancreas, in response to the elevation of glycemia after eating, and low insulin plasma levels enhance the production of the orexigenic neuropeptide-Y (NPY) in the hypothalamus, triggering hunger.[23] Of note, animal studies have shown that propofol administration is associated with a rise in insulin production compared with halogenated drugs.[25,26] This may be explained, in part, by the fact that propofol contains 10% fatty acids, and central sensing of fatty acids by the hypothalamus enhances insulin production.[27]

Leptin is mainly produced by white adipose tissue and is positively correlated with fat mass and nutrient intake.[28] It decreases food intake in mice via activation of central neurons implicated in feeding behaviour.[24] Ghrelin is produced in the fundus of the stomach and its production is enhanced by fasting.[29] It is currently the only gut hormone with known orexigenic proprieties, and high plasma levels induce NPY production.[23] In our study, no between-group differences were observed in leptin- and ghrelin plasma levels and changes in plasma levels of the three hormones within each group showed similar fluctuations for propofol and sevoflurane, with slight to moderate variations over the time. To the best of our knowledge, no other study has explored the impact of anesthesia on these hormones.

Several limitations of our study should be acknowledged. The study focused on procedures performed between 08:00 and 10:00 a.m. (to limit potential confounding related to duration of fasting) and this may limit the generalizability of our data. We also cannot exclude the possibility that the administration of hormones before oocyte puncture may have altered patients' sensations of hunger, even though the randomization process achieved a homogeneous distribution of patients who received either GnRH agonists or antagonists. We also cannot exclude the possibility that the relatively brief duration of anesthesia our patients were exposed to limited the potential effects of anesthetic drugs on hunger, notwithstanding the anecdotal evidence that propofol enhances hunger in outpatients undergoing brief endoscopic procedures.[11,12] A potentially confounding variable was the difference in duration of anesthesia between groups: patients in the sevoflurane group had a somewhat longer duration of anesthesia including a higher cumulative dose of remifentanil, which could have impacted feeding behaviour. As sevoflurane is expected to reduce the sensation of hunger,[9,10] we anticipate that this difference in anesthesia time would have (if anything) exaggerated any pro-feeding influence of propofol. Another potentially confounding variable is the effect of other drugs administrated to both groups, including paracetamol, hydroxyzine, dexamethasone, droperidol, and remifentanil. Although opioids do not appear to modify appetite in cancer patients,[30] the endogenous opioid-cannabinoid system is implicated in the reward system for food intake,[31] and we cannot rule out a confounding effect of remifentanil on hunger. Moreover, opioids can induce nausea and/or vomiting, which may adversely affect hunger.[32] Finally, as this study was performed only on female patients, the relevance of these findings to males is questionable.

In summary, compared with sevoflurane, propofol did not accelerate the recovery of hunger after outpatient minor surgery. Moreover, propofol was not distinguished by its effect on other clinical or biological parameters associated with food intake.

Author contributions *Emmanuel Besnier* designed and conducted the study, and wrote the manuscript. *Anne Perdrix* measured ghrelin, leptin, and insulin plasma levels. *André Gillibert* performed statistical analyses and critically revised the manuscript. *Jean Selim*, *Benoit Froëmer*, and *Antoine Ghemired* recruited the patients and performed follow-up. *Benoit Berby* and *Nathalie Rives* performed gynecological procedures. *Bertrand Dureuil*, *Thomas Clavier*, and *Vincent Compère* contributed to study design and supervision, and critically revised the manuscript.

Acknowledgements The authors are grateful to Nikki Sabourin-Gibbs (English native speaker), Rouen University Hospital, for her help in editing the manuscript.

Conflicts of interest None.

Funding statement This trial was supported, conducted and funded by the *Direction de la Recherche Clinique et de l'Innovation* of the *CHU-Hôpitaux de Rouen*, France (AOJC 2014-04).

Editorial responsibility This submission was handled by Dr. Steven Backman, Associate Editor, *Canadian Journal of Anesthesia.*

APPENDIX Postanesthetic discharge scoring system (PADSS) score[1]

1. Vital signs (blood pressure, heart rate, respiratory rate)

   2 = within 20% of preoperative value
   1 = 20–40% of preoperative value
   0 = > 40% of preoperative value

2. Activity and mental status

   2 = oriented AND has a steady gait
   1 = oriented OR has a steady gait
   0 = neither

3. Pain, nausea and/or vomiting

   2 = minimal
   1 = moderate, having required treatment
   0 = severe, currently requiring treatment

4. surgical bleeding

   2 = minimal
   1 = moderate
   0 = severe

5. Intake and output

   2 = has had *per os* fluids and voided
   1 = has had fluids or voided
   0 = neither

   Score $\geq$ 9/10 for discharge from hospital

Adapted from *Chung F, Chan VW, Ong D*. A post-anesthetic discharge scoring system for home readiness after ambulatory surgery. J Clin Anesth 1995; 7: 500-6.[1]

References

1. *Chung F*, *Chan VW*, *Ong D*. A post-anesthetic discharge scoring system for home readiness after ambulatory surgery. J Clin Anesth 1995; 7: 500-6.
2. *Charoenkwan K*, *Matovinovic E*. Early versus delayed oral fluids and food for reducing complications after major abdominal gynaecologic surgery. Cochrane Database Syst Rev 2014; DOI: https://doi.org/10.1002/14651858.CD004508.pub4.
3. *Minig L*, *Biffi R*, *Zanagnolo V*, *et al*. Early oral versus "traditional" postoperative feeding in gynecologic oncology patients undergoing intestinal resection: a randomized controlled trial. Ann Surg Oncol 2009; 16: 1660-8.
4. *Minig L*, *Biffi R*, *Zanagnolo V*, *et al*. Reduction of postoperative complication rate with the use of early oral feeding in gynecologic oncologic patients undergoing a major surgery: a randomized controlled trial. Ann Surg Oncol 2009; 16: 3101-10.
5. *Wren AM*, *Seal LJ*, *Cohen MA*, *et al*. Ghrelin enhances appetite and increases food intake in humans. J Clin Endocrinol Metab 2001; DOI: https://doi.org/10.1210/jcem.86.12.8111.
6. *Stanley S*, *Wynne K*, *McGowan B*, *Bloom S*. Hormonal regulation of food intake. Physiol Rev 2005; 85: 1131-58.
7. *Suzuki K*, *Simpson KA*, *Minnion JS*, *Shillito JC*, *Bloom SR*. The role of gut hormones and the hypothalamus in appetite regulation. Endocr J 2010; 57: 359-72.
8. *Señarís RM*, *Trujillo ML*, *Navia B*. Interleukin-6 regulates the expression of hypothalamic neuropeptides involved in body weight in a gender-dependent way. J Neuroendocrinol 2011; 23: 675-86.
9. *Besnier E*, *Clavier T*, *Tonon MC*, *et al*. Anesthetic drugs modulate feeding behavior and hypothalamic expression of the POMC polypeptide precursor and the NPY neuropeptide. BMC Anesthesiol 2018; DOI: https://doi.org/10.1186/s12871-018-0557-x.
10. *Grouzmann E*, *Borgeat A*, *Fathi M*, *Gaillard R*, *Ravussin P*. Plasma and cerebrospinal fluid concentrations of neuropeptide Y, serotonin, and catecholamines in patients under propofol or isoflurane anesthesia. Can J Physiol Pharmacol 2000; 78: 100-7.
11. *Serin S*, *Elibol O*, *Sungurtekin H*, *Gonullu M*. Comparison of halothane/thiopental and propofol anesthesia for strabismus surgery. Ophtalmologica 1993; 213: 224-7.
12. *Metrot J*, *Vigreux JM*. Blood glucose and propofol in outpatient anaesthesia. Ambul Surg 1993; 2: 101-2.
13. *Apfel CC*, *Korttila K*, *Abdalla M*, *et al*. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med 2004; 350: 2441-51.
14. *Parker BA*, *Sturm K*, *MacIntosh CG*, *Feinle C*, *Horowitz M*, *Chapman IM*. Relation between food intake and visual analogue scale ratings of appetite and other sensations in healthy older and young subjects. Eur J Clin Nutr 2004; 58: 212-8.
15. *Flint A*, *Raben A*, *Blundell JE*, *Astrup A*. Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. Int J Obes Relat Metab Disord 2000; 24: 38-48.
16. *Westfall PH*. *Young SS*. Resampling-Based Multiples Testing: Examples and Methods for p-Value Adjustment. John Wiley & Sons; 1993. p. 47-53.
17. *Zhuang CL*, *Ye XZ*, *Zhang CJ*, *Dong QT*, *Chen BC*, *Yu Z*. Early versus traditional postoperative oral feeding in patients undergoing elective colorectal surgery: a meta-analysis of randomized clinical trials. Dig Surg 2013; 30: 225-32.
18. *Tepaske R*, *Velthuis H*, *Oudemans-van Straaten HM*, *et al*. Effect of preoperative oral immune-enhancing nutritional supplement on patients at high risk of infection after cardiac surgery: a randomised placebo-controlled trial. Lancet 2001; 358: 696-701.
19. *Sallé A*, *Dalmayrac E*, *Baufreton C*. Early postoperative undernutrition following aortic valve replacement surgery. Clin Nutr ESPEN 2018; 26: 84-90.
20. *Kmiec Z*. Aging and peptide control of food intake. Curr Protein Pept Sci 2011; 12: 271-9.
21. *Eggersdorfer M*, *Akobundu U*, *Bailey RL*, *et al*. Hidden hunger: solutions for America's aging populations. Nutrients 2018; DOI: https://doi.org/10.3390/nu10091210.
22. *Merriweather JL*, *Griffith DM*, *Walsh TS*. Appetite during the recovery phase of critical illness: a cohort study. Eur J Clin Nutr 2018; 72: 986-92.
23. *Blouet C*, *Schwartz GJ*. Hypothalamic nutrient sensing in the control of energy homeostasis. Behav Brain Res 2010; 209: 1-12.
24. *Millington GW*. The role of proopiomelanocortin (POMC) neurones in feeding behaviour. Nutr Metab (Lond) 2007; DOI: https://doi.org/10.1186/1743-7075-4-18.
25. *Sato K*, *Kitamura T*, *Kawamura G*, *et al*. Glucose use in fasted rats under sevoflurane anesthesia and propofol anesthesia. Anesth Analg 2013; 117: 627-33.
26. *Li X*, *Kitamura T*, *Kawamura G*, *et al*. Comparison of mechanisms underlying changes in glucose utilization in fasted rats anesthetized with propofol or sevoflurane: hyperinsulinemia is exaggerated by propofol with concomitant insulin resistance induced by an acute lipid load. Biosci Trends 2014; 8: 155-62.
27. *Migrenne S*, *Le Foll C*, *Levin BE*, *Magnan C*. Brain lipid sensing and nervous control of energy balance. Diabetes Metab 2011; 37: 83-8.
28. *Brennan AM*, *Mantzoros CS*. Drug insight: the role of leptin in human physiology and pathophysiology–emerging clinical applications. Nat Clin Pract Endocrinol Metab 2006; 2: 318-27.
29. *Inui A*, *Asakawa A*, *Bowers CY*, *et al*. Ghrelin, appetite, and gastric motility: the emerging role of the stomach as an endocrine organ. FASEB J 2004; 18: 439-56.

30. *Wiffen PJ*, *Derry S*, *Moore RA*. Impact of morphine, fentanyl, oxycodone or codeine on patient consciousness, appetite and thirst when used to treat cancer. Cochrane Database Sys Rev 2014; DOI: https://doi.org/10.1002/14651858.CD011056.pub2.
31. *Olszewski PK*, *Alsiö J*, *Schiöth HB*, *Levine AS*. Opioids as facilitators of feeding: can any food be rewarding? Physiol Behav 2011; 104: 105-10.
32. *Smith HS*, *Laufer A*. Opioid induced nausea and vomiting. Eur J Pharmacol 2014; 722: 67-78.