Feasibility of closed-loop co-administration of propofol and remifentanil guided by the bispectral index in obese patients: a prospective cohort comparison†

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Background. We used an automated bispectral index (BIS)-guided dual-loop controller to determine propofol and remifentanil requirements during general anaesthesia in obese and lean surgical patients.

Methods. Obese patients, BMI >35 kg m\(^{-2}\), and lean patients (<25 kg m\(^{-2}\)) having laparoscopic procedures were prospectively evaluated in this multicentre single-blind study. The automated controller targeted BIS between 40 and 60 by adjusting propofol and remifentanil administration. Propofol and remifentanil consumptions were calculated using both total body weight (TBW) and ideal body weight (IBW). Results are expressed as medians (inter-quartile range).

Results. Thirty obese [BMI = 43 (40–49) kg m\(^{-2}\)] and 29 lean [BMI = 23 (21–25) kg m\(^{-2}\)] patients completed the study. BIS was between 40 and 60 during 84 (69–91)% vs 85 (78–92)% of the anaesthetic time, \(P = 0.46\). The amount of propofol given during induction [1.2 (1.1–1.6) vs 1.3 (1.0–1.7) mg kg\(^{-1}\), \(P = 0.47\)] and maintenance [5.2 (4.1–6) vs 5.3 (4.7–6.4) mg kg\(^{-1}\) h\(^{-1}\), \(P = 0.39\)] calculated using TBW was similar between the two groups. The dual-loop controller delivered half as much remifentanil to the obese patients during induction [1.0 (0.8–1.6) vs 2.2 (1.5–2.7) \(\mu\)g kg\(^{-1}\) h\(^{-1}\), \(P<0.001\)] and maintenance [0.12 (0.07–0.16) vs 0.25 (0.17–0.29) \(\mu\)g kg\(^{-1}\) min\(^{-1}\), \(P<0.001\)] calculated using TBW. But when remifentanil consumption was calculated using IBW, the amounts were similar during induction at 2.2 (1.6–3.5) vs 2.0 (1.6–3.0) \(\mu\)g kg\(^{-1}\) IBW, \(P = 0.48\), and during maintenance at 0.26 (0.16–0.34) vs 0.27 (0.18–0.33) \(\mu\)g kg\(^{-1}\) min\(^{-1}\), \(P = 0.50\).

Conclusions. The amount of propofol–remifentanil administered by the controller is consistent with current knowledge, propofol is best dosed using TBW whereas remifentanil is best dosed using IBW.

Clinical trial registration. NCT00779844.

Keywords: anaesthesia; bispectral index; closed-loop; i.v. anaesthetics; obesity; propofol; remifentanil

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A growing fraction of the world’s population is obese\(^{1}\) and obese patients are considered as high anaesthetic risk patients.\(^{2}\) Optimizing i.v. anaesthetic titration represents a challenge for the clinician because of obesity-related modifications in drug pharmacokinetics (PK) and possibly pharmacodynamics (PD).\(^{3}\) Dosing propofol based on actual or total body weight (TBW) may result in excessive drug administration\(^{4}\) during maintenance, whereas dosing based on ideal body weight (IBW) may result in inadequate drug administration during induction.\(^{3}\) It is similarly unclear how best to approach remifentanil dosing in obese patients.

One approach to dosing is to conduct PK analyses in the obese and then introduce a weight-specific PK model in target-controlled infusion (TCI) systems. For lean patients, the PK model...
of Schnider and colleagues6 for propofol is used in routine practice. But for obese patients, this PK model overestimates propofol clearance during maintenance because of a paradoxically decreased value of lean body mass calculated by the James’ formula which appears to be flawed at high values of TBW.8 9 For remifentanil, the lean body mass used in the PK model of Minto and colleagues10 is calculated using the same formula.7 The lean body mass is an important covariate of several PK parameters in the Minto and colleagues model,10 in particular the central volume, the rapid peripheral volume of distribution, and the metabolic clearance were underestimated with the consequence that remifentanil is underdosed in obese patients.11 12 Finally, for obese patients, specific propofol PK models have been developed13 14 with age integrated as a relevant covariate.14 The PK model of Minto can similarly be improved by calculating the true value of lean body mass using the formula of Janmahasatian and colleagues12 15 or by calculating ‘fictitious height’.11 However, one difficulty with an isolated PK approach is that PD factors may also vary in lean or obese patients.16

An alternative strategy is to titrate drug administration to a direct measure of hypnotic effect, for example, frontal electro-cortical activity as determined by the bispectral index (BIS).17 18 Moreover, the BIS change is sensitive for detecting the deficit of antinociception: noxious stimuli may cause electro-cortical activation such as haemodynamic change allowing the titration of analgesia.19 We have developed and validated a dual closed-loop controller that automatically co-administers propofol and remifentanil solely guided by the BIS.20 The closed-loop system has a cascade structure including a proportional-integral-derivative controller which steers a TCI system. Recently, the controller was used as an unbiased method for the determination of anaesthetic requirements in surgical patients,21 22 and this reproducible method has the potential to accurately determine anaesthetic requirements in obese patients.

We thus used our BIS-guided dual-loop controller to determine propofol and remifentanil requirements during induction and maintenance of general anaesthesia in obese and lean surgical patients. In particular, we evaluated propofol and remifentanil consumption when the same controller was used in both groups without modification of the PK models or weight adjustment methods.

### Methods

Our prospective two-centre, single-blind, cohort comparison with adaptive matching was approved by the French Ethics Committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale, Hôpital A. Paré, Boulogne Billancourt, France, N° 08 03 11). It was also approved by the French National Regulatory Office (Agence Française de Sécurité Sanitaire des Produits de Santé, N° A80314-53). This study was registered at ClinicalTrials.gov (NCT007798B44). Written informed consent was obtained from participating patients.

We enrolled adults undergoing elective upper-abdominal or bariatric laparoscopic procedures expected to last >60 min requiring general anaesthesia with tracheal intubation without combined regional anaesthesia. All were ASA physical status I–III. Exclusion criteria included psychiatric illness, supraspinal neurological disorders, a pacemaker, symptomatic gastro-oesophageal reflux, expected difficult airway management, or planned awake fibreoptic intubation. Obese patients were enrolled at the Hôpital Européen Georges Pompidou (Paris, France) and lean patients were enrolled at the Hôpital Foch (Suresnes, France).

Patients with a BMI >35 kg m⁻² were enrolled in the obese group. Matched patients with a BMI <25 kg m⁻² were enrolled in the lean group. The matching criteria were age (±10 yr) and sex. A preliminary analysis reported that the sex ratio was one male for four females for the obese patients and one male for one female in lean patients undergoing elective upper-abdominal laparoscopic procedures. Thus, we decided to enrol one lean man for each obese man, and two lean women and one lean man for every three obese women allowing the inclusion of one lean patient within 30 days after the inclusion of one obese patient.

### Procedures

No premedication was used except for 150 mg of cimetidine in the obese patients. Propofol and remifentanil were administered by identical closed-loop automated systems. Automated control was used during induction and throughout maintenance of general anaesthesia. TBW was set in the TCI systems of the controller using the PK model of Schnider and colleagues5 for propofol and the PK model of Minto and colleagues10 for remifentanil in both groups.

The controller modifies the calculated effect-site drug concentrations using the TBW in both groups according to intraoperative BIS variations (Covidien, Dublin, Ireland). The dual-loop assumption is that small fluctuations of BIS are related to the intensity of noxious stimuli.19 Small variations in BIS thus provoked changes only to remifentanil; but when the variation was large, both remifentanil and propofol were modified. The controller has previously been validated in lean patients in a randomized controlled study.20 Details of the controller are provided in the Appendix. All investigators received a full day of training in the use of the automated controller at the Hôpital Foch, and were able to override the automated system if necessary, or to switch between automated and manual control.

Upon arrival in the operating theatre, a dedicated i.v. cannula was inserted and routine monitoring started. Neuromuscular function at the adductor pollicis was monitored after loss of consciousness. Before induction, a BIS electrode (Zip Prep, Covidien) was positioned on the patient’s forehead and connected to either an A-2000 XP (version 3.11) BIS monitor or a BIS M-Module (GE-Healthcare S5™, Helsinki, Finland).

Before induction, patients were pre-oxygenated with 100% oxygen through a face mask. In obese patients, a PEEP at 10 cm H₂O was applied until end-tidal oxygen saturation >92% was obtained. In both groups, investigators chose the initial propofol effect-site target concentration according to their clinical judgement; in contrast, the initial remifentanil effect-site...
target concentration was determined by the controller. Lean patients were given atracurium to facilitate tracheal intubation, whereas a rapid-sequence induction with succinylcholine was used in obese patients.

After tracheal intubation, the lungs were mechanically ventilated with 40% inspired oxygen without nitrous oxide and a PEEP at 5 cm H2O. Atracurium was given to provide muscle relaxation throughout surgery in both groups. Other than administration of the study drugs, patient management was based on current standards of care. No specific recommendations were given for the treatment of haemodynamic abnormalities.

Approximately 45 min before the presumed end of surgery, i.v. analgesics were given to provide postoperative pain relief. Morphine, paracetamol, nefopam, or non-steroidal anti-inflammatory drugs were given at the discretion of the physician. In both weight groups, propofol and remifentanil were stopped simultaneously upon completion of surgery and all patients were ventilated with 100% oxygen before tracheal extubation.

Vasopressor or anti-hypertensive use was recorded. Recall of intraoperative events was evaluated by a standardized interview performed in the post-anaesthesia care unit and on the second or third postoperative day.24

Statistical analyses

Induction of anaesthesia was defined by the time elapsed between the beginning of propofol and remifentanil administration until BIS was <60 for 30 s. The maintenance phase extended from this point until propofol and remifentanil administration was discontinued at the end of surgery.

The primary outcomes were propofol and remifentanil consumption during induction and maintenance of general anaesthesia. Consumption of each drug during each period was calculated in terms of TBW and in terms of IBW according to the following formula: IBW (kg) = 45.4 (49.9 if male) + 0.89 × (height in cm − 152.4).25

Secondary outcomes included the fraction of time in which patients demonstrated adequate anaesthesia, defined as BIS between 40 and 60 (BIS40–60), deep anaesthesia (BIS <40), and light anaesthesia (BIS >60). Excessive anaesthesia was defined as the occurrence of suppression ratio with suppression ratio >10% lasting at least 1 min.26 Data from the BIS monitor were recorded every 5 s.

In a previous study of lean patients during maintenance of general anaesthesia, propofol consumption was 4.7 (1.6) mg kg⁻¹ h⁻¹ using our automated controller; therefore, in obese

Fig 1 Trial profile.
patients, we expected that the controller would decrease propofol consumption by 30% calculated using the TBW. A minimum of 28 subjects per group was thus required to provide a 90% power for a two-sided error of 5%. Under the assumption that some patients would be excluded for various reasons, we planned a total of 64 patients.

Categorical variables, expressed as numbers and frequencies, were compared using Fisher’s exact test as appropriate. Continuous variables were described as the median and interquartile range (IQR) and compared using the Mann–Whitney U-test. Probability values of <0.05 using two-tailed tests were considered statistically significant. Data analysis was performed using IBM-SPSS® version 20 (IBM-SPSS Science, Inc., Chicago, IL, USA).

**Results**

Among 70 patients who were approached, 64 were recruited between January 2009 and September 2011. Usable data were obtained from 30 patients in the obese group and 29 patients in the lean group (Fig. 1). Baseline characteristics were similar except for TBW and BMI. In the obese group, only one patient among the 30 had a BMI $\geq 35$ kg m$^{-2}$. The initial effect-site target concentration of propofol chosen by the investigators was similar in the obese \([2.5 \, (2.0 - 4.5) \, \mu g \, ml^{-1}]\) and lean \([2.1 \, (1.0 - 4.0) \, \mu g \, ml^{-1}]\) groups, $P=0.21$

**Table 1** Baseline patient characteristics. Results expressed as median (inter-quartile range) or number (%); TBW, total body weight; IBW, ideal body weight; obese, BMI $> 35$ kg m$^{-2}$; lean, BMI $< 35$ kg m$^{-2}$

<table>
<thead>
<tr>
<th></th>
<th>Obese (n=30)</th>
<th>Lean (n=29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>36 (29–49)</td>
<td>42 (34–55)</td>
<td>0.08</td>
</tr>
<tr>
<td>Sex ratio (male/female)</td>
<td>5/25</td>
<td>10/19</td>
<td>0.13</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165 (160–170)</td>
<td>168 (160–173)</td>
<td>0.15</td>
</tr>
<tr>
<td>Weight or TBW (kg)</td>
<td>43 (40–49)</td>
<td>65 (57–72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg m$^{-2}$)</td>
<td>43 (40–49)</td>
<td>65 (57–72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IBW (kg)</td>
<td>57 (52–64)</td>
<td>59 (52–64)</td>
<td>0.21</td>
</tr>
<tr>
<td>ASA physical status III</td>
<td>3 (10)</td>
<td>1 (3)</td>
<td>0.61</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (10)</td>
<td>2 (7)</td>
<td>0.72</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (13)</td>
<td>1 (3)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

**Fig 2** BIS values, effect-site concentration of propofol (Ce$_{prop}$) calculated using the model of Schnider and colleagues$^6$ and remifentanil (Ce$_{rem}$) calculated using the model of Minto and colleagues$^{10}$ from induction to the discontinuation of these drugs. Data are given individually and as median values (green) with 10th and 90th percentiles with a moving average filter of 1 min duration for graphical representation. Obese, patients with BMI $> 35$ kg m$^{-2}$; lean, patients with BMI $< 35$ kg m$^{-2}$. 

![BIS values, effect-site concentration of propofol (Ce$_{prop}$) calculated using the model of Schnider and colleagues$^6$ and remifentanil (Ce$_{rem}$) calculated using the model of Minto and colleagues$^{10}$ from induction to the discontinuation of these drugs. Data are given individually and as median values (green) with 10th and 90th percentiles with a moving average filter of 1 min duration for graphical representation. Obese, patients with BMI $> 35$ kg m$^{-2}$; lean, patients with BMI $< 35$ kg m$^{-2}$.

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Propofol and remifentanil consumption in obese and lean patients

and induction data were presented in Table 2. The median BIS values from induction to propofol and remifentanil discontinuation are presented in Figure 2.

During maintenance, propofol consumption calculated using the TBW was similar in each group (Table 3 and Fig. 3) but different when calculated using the IBW (Fig. 3). Obese patients used half as much remifentanil as the lean patients when dose was expressed in terms of IBW. However, remifentanil consumption during maintenance anaesthesia was similar in each weight group when dose was expressed in terms of IBW (Table 3 and Fig. 3). The use of ephedrine and anti-hypertensive therapy was similar in each group (Table 3). No cases of awareness with recall were reported.

The percentage of adequate anaesthesia and of deep or excessive anaesthesia was similar in the two groups, suggesting that the anaesthetic effect was similar in each weight group (Table 4).

Discussion

Automated administration of anaesthetic agents guided by electro-cortical activity is well established27 and has been successfully used during major surgery in patients with various co-morbidities,20 26 28–32 during cardiac surgery in adults33 and paediatric patients,34 during lung transplantation,15 during pheochromocytoma resection,36 during rigid bronchoscopy,37 for deep sedation in intensive care units,38 and for sedation in paediatric patients.39 The use of an automated controller reduces episodes of excessive anaesthesia, and enhances predictability of tracheal extubation in lean patients.20 28 We used BIS-guided automatic drug administration because it is an objective way to determine anaesthetic requirement which avoids largely unjustified assumptions about PK/PD that would otherwise be necessary when comparing drug use in obese and lean patients. Specifically, because the system was based on individual patient responses, the amounts of propofol and remifentanil given being based on individual requirements, it was probably independent of the underlying PK model but related to the gain constant of the controller. That the fraction of time with deep or excessive anaesthesia, the amount of burst suppression, and the use of vasopressors was similar in the obese and lean patients indicates that the controller provided a comparable anaesthetic effect in the obese and lean patients.

Propofol requirements, based on TBW, were similar in obese and lean patients during induction of anaesthesia. The amount of propofol used during anaesthetic induction was 1.2 (1.1–1.6) mg kg\(^{-1}\) which was only slightly < 1.6 (0.2) mg kg\(^{-1}\) dose previously reported to achieve a BIS < 60 in 95% of patients.40 It is towards the lower end of the propofol dose range for anaesthetic induction which ranges from 0.9 (0.1)40 to 2.5 mg kg\(^{-1}\).5 This great variability of induction doses probably relates to differences in the definition of induction (clinical signs41 or to achieve a BIS value);40 the propofol administration methods (bolus,5  continuous infusion,42 or TCI);43 the opioid used (bolus of fentanyl,5 43–45 remifentanil in continuous infusion44, or TCI);13 how much opioid was given (15042 to 250 mg kg\(^{-1}\) or 241 to 345 mg kg\(^{-1}\) of fentanyl bolus), and when it was given (before,40 41 43 44 simultaneously,13 or after5 42 propofol infusion) (Table 5).

### Table 2

**Induction phase. Data are presented as median (inter-quartile range) or number (%) of total patients of each group; obese, BMI > 35 kg m\(^{-2}\); lean, BMI < 35 kg m\(^{-2}\); TBW, total body weight; IBW, ideal body weight. Induction was defined as the time elapsed from the beginning of propofol administration until BIS was < 60 for 30 s. Cormack–Lehane III and IV: only epiglottis seen, none of the glottis seen, or neither the glottis nor the epiglottis seen during direct laryngoscopy.**

<table>
<thead>
<tr>
<th></th>
<th>Obese (n = 30)</th>
<th>Lean (n = 29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (s)</td>
<td>189 (158–253)</td>
<td>182 (132–246)</td>
<td>0.61</td>
</tr>
<tr>
<td>Propofol (mg kg(^{-1}) IBW)</td>
<td>1.2 (1.1–1.6)</td>
<td>1.3 (1.0–1.7)</td>
<td>0.47</td>
</tr>
<tr>
<td>Remifentanil ((\mu)g kg(^{-1}) IBW)</td>
<td>2.2 (1.6–3.5)</td>
<td>2.0 (1.6–3.0)</td>
<td>0.48</td>
</tr>
<tr>
<td>Ephedrine boluses</td>
<td>6 (20)</td>
<td>3 (11)</td>
<td>0.48</td>
</tr>
<tr>
<td>Occurrence of suppression ratio</td>
<td>2 (6)</td>
<td>2 (7)</td>
<td>1</td>
</tr>
<tr>
<td>Cormack–Lehane III and IV</td>
<td>1 (3)</td>
<td>2 (7)</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Remifentanil</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (min)</td>
<td>147 (98–211)</td>
<td>106 (97–152)</td>
<td>0.09</td>
</tr>
<tr>
<td>Median (mg kg(^{-1}) h(^{-1}) IBW)</td>
<td>5.2 (4.1–6)</td>
<td>5.3 (4.7–6.4)</td>
<td>0.39</td>
</tr>
<tr>
<td>Modifications per h</td>
<td>27 (25–36)</td>
<td>27 (21–30)</td>
<td>0.29</td>
</tr>
<tr>
<td>Median effect-site ((\mu)g ml(^{-1}))</td>
<td>2.1 (1.8–2.4)</td>
<td>2.1 (1.8–2.5)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

### Table 3

**Maintenance phase. Data are presented as median (inter-quartile range) or number (%) of total patients of each group; obese, BMI > 35 kg m\(^{-2}\); lean, BMI < 35 kg m\(^{-2}\); TBW, total body weight; IBW, ideal body weight; time to tracheal extubation was defined as discontinuation of propofol and remifentanil until extubation.**

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<th>Obese (n = 30)</th>
<th>Lean (n = 29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>147 (98–211)</td>
<td>106 (97–152)</td>
<td>0.09</td>
</tr>
<tr>
<td>Propofol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (mg kg(^{-1}) h(^{-1}) IBW)</td>
<td>5.2 (4.1–6)</td>
<td>5.3 (4.7–6.4)</td>
<td>0.39</td>
</tr>
<tr>
<td>Remifentanil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median ((\mu)g kg(^{-1}) min(^{-1}) IBW)</td>
<td>0.12 (0.07–0.16)</td>
<td>0.25 (0.17–0.29)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 2: Induction phase. Data are presented as median (inter-quartile range) or number (%) of total patients of each group; obese, BMI > 35 kg m\(^{-2}\); lean, BMI < 35 kg m\(^{-2}\); TBW, total body weight; IBW, ideal body weight. Induction was defined as the time elapsed from the beginning of propofol administration until BIS was < 60 for 30 s. Cormack–Lehane III and IV: only epiglottis seen, none of the glottis seen, or neither the glottis nor the epiglottis seen during direct laryngoscopy.

Table 3: Maintenance phase. Data are presented as median (inter-quartile range) or number (%) of total patients of each group; obese, BMI > 35 kg m\(^{-2}\); lean, BMI < 35 kg m\(^{-2}\); TBW, total body weight; IBW, ideal body weight; time to tracheal extubation was defined as discontinuation of propofol and remifentanil until extubation.
Propofol requirements, based on TBW, were also similar in obese and lean patients during anaesthetic maintenance. In both weight groups, propofol consumption was \( \approx 5 \text{ mg kg}^{-1} \text{ h}^{-1} \) (Fig. 3A) which is consistent with previous recommendations for obese patients.\(^{45}\) 5.5–7.0 mg [(kg of TBW \( 70^{-1} \))\(^{0.72}\)] h\(^{-1}\) or 4–6 mg kg\(^{-1}\) h\(^{-1}\). The propofol consumption reported during maintenance anaesthesia varied from 2 mg kg\(^{-1}\) h\(^{-1}\) when combined with regional anaesthesia and nitrous oxide\(^{18}\) to 6.1 (1.8) mg kg\(^{-1}\) h\(^{-1}\) during open bariatric surgery.\(^{46}\) Table 5 summarizes propofol consumption in different clinical studies where consumption was related to the method of analgesia, type of surgery, or the use of brain monitoring. Our key result, though, is that propofol requirements, expressed as a function of TBW, are almost identical in obese and lean patients related to the increase in cardiac output, distribution volume, and propofol clearance by the liver.

<table>
<thead>
<tr>
<th>TBW Consumption</th>
<th>IBW Consumption</th>
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<tbody>
<tr>
<td><strong>Obese</strong></td>
<td><strong>Lean</strong></td>
</tr>
<tr>
<td>5.5–7.0 mg kg(^{-1}) h(^{-1})</td>
<td>4–6 mg kg(^{-1}) h(^{-1})</td>
</tr>
</tbody>
</table>

Fig 3 Propofol and remifentanil consumptions calculated using TBW (A) and IBW (B). Obese, patients with BMI > 35 kg m\(^{-2}\); lean, patients with BMI < 35 kg m\(^{-2}\); blue histograms represent the obese group and green histograms represent the lean group. Normal distribution curve for obese (solid line) and lean (dashed line) groups. *P < 0.0001.
correlated to the TBW. Clinicians should thus dose propofol in obese patients just as they usually do, based on TBW.

Remifentanil is a short-acting opioid agonist with an elimination half-life that is independent of infusion duration. The dose of remifentanil for anaesthetic maintenance in obese patients ranges from 0.12 to 0.43 µg kg⁻¹ min⁻¹ calculated as a function of TBW (Table 5). Remifentanil consumption in obese patients, calculated using TBW, was half what it was in the lean patients during both induction and maintenance. In contrast, the dose was nearly the same in each weight group when expressed in terms of lean body mass. This result is unsurprising, given that lean body mass is an important covariate for distribution volumes and clearances of remifentanil. Our result extends previous PK analyses in that it is based on individual patient responses and thus includes both PK and potential PD effects of obesity. Finally, this study is in agreement with a previous study that the remifentanil is best dosed using IBW.

A limitation of our study is that the surgical procedures differed in the two groups. However, the magnitude and duration of the operations was comparable and it seems unlikely that anaesthetic requirement would otherwise much differ from similar procedures.

Remifentanil titration was guided by electro-cortical activity rather than by haemodynamic changes, which are more often used in clinical practice. We chose BIS because painful stimulation does not reliably provoke haemodynamic responses in patients treated by anti-hypertensive therapy; furthermore, haemodynamic responses can be modified by vasopressor use, various preoperative or intraoperative treatments, blood loss, fluid administration, arrhythmia, heart failure, or manipulation of a great vessel. In particular, during laparoscopic procedures, a significant increase in mean arterial pressure has been reported after the increase in intra-abdominal pressure which is a stimulator of vasopressin release or hypercapnia induced by the CO₂ insufflations. BIS guidance is thus more likely than arterial pressure or heart rate to identify true anaesthetic requirement during a laparoscopic procedure.

A hypnotic like propofol and an analgesic like remifentanil can be combined in various ways. The relationship between the two study drugs in this study was determined by parameters...

Table 4: Efficiency of the control system during maintenance of anaesthesia. Data are presented as median (inter-quartile range) or number (%) of total patients of each group. Obese, BMI > 35 kg m⁻²; lean, BMI < 35 kg m⁻²; BIS, bispectral index. BIS₄₀₆₀ adequate anaesthesia or percentage of time in which the BIS value was between 40 and 60 during maintenance; BIS₄₀₆₀ percentage of time in which the BIS value was below a value of 40; BIS₆₀₉₀% burst suppression; suppression ratio > 10% for at least 1 min

<table>
<thead>
<tr>
<th></th>
<th>Obese (n=30)</th>
<th>Lean (n=29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIS₄₀₆₀</td>
<td>84 (69–91)</td>
<td>85 (78–92)</td>
<td>0.46</td>
</tr>
<tr>
<td>BIS₄₀₆₀</td>
<td>14 (7–26)</td>
<td>11 (6–16)</td>
<td>0.37</td>
</tr>
<tr>
<td>BIS₆₀₉₀₆₀₉₀⁵⁰</td>
<td>2 (1–4)</td>
<td>4 (2–6)</td>
<td>0.021</td>
</tr>
<tr>
<td>Burst suppression</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 5: Propofol and remifentanil consumption in obese patients. Data are presented as median (inter-quartile range), means (SDs), or numbers (%). TBW, total body weight; n, number of patients; BIS, bispectral index; CSM, cerebral state monitor; N₂O, nitrous oxide; NA, not available

<table>
<thead>
<tr>
<th>Study</th>
<th>Induction (mg kg⁻¹)</th>
<th>Maintenance (mg kg⁻¹ h⁻¹)</th>
<th>Remifentanil (µg kg⁻¹)</th>
<th>Maintenance (µg kg⁻¹ min⁻¹)</th>
<th>Brain monitor</th>
<th>Surgery</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current study</td>
<td>1.2 (1.1–1.6)</td>
<td>5.2 (4.1–6)</td>
<td>1.0 (0.8–1.6)</td>
<td>0.12 (0.07–0.16)</td>
<td>BIS</td>
<td>Laparoscopic</td>
<td>30</td>
</tr>
<tr>
<td>Lam and colleagues</td>
<td>2</td>
<td>NA</td>
<td>Fentanyl</td>
<td></td>
<td>BIS</td>
<td>Laparoscopic</td>
<td>18</td>
</tr>
<tr>
<td>de la Fuente and colleagues</td>
<td>0.9 (0.1) to 1.6 (0.2)</td>
<td>NA</td>
<td>Fentanyl</td>
<td></td>
<td>BIS</td>
<td>NA</td>
<td>35</td>
</tr>
<tr>
<td>Echevarria and colleagues</td>
<td>1.4 (1.3–1.5) to 2.4 (2.2–2.5)</td>
<td>NA</td>
<td>Fentanyl</td>
<td>BIS</td>
<td>NA</td>
<td>Bariatric</td>
<td>30</td>
</tr>
<tr>
<td>Ingrande and colleagues</td>
<td>1.84 (0.33)</td>
<td>NA</td>
<td>Fentanyl</td>
<td></td>
<td>No</td>
<td>Bariatric</td>
<td>30</td>
</tr>
<tr>
<td>van Kralingen and colleagues</td>
<td>350 mg bolus or 2.5</td>
<td>4.8 (1.5)</td>
<td>Fentanyl</td>
<td>0.12</td>
<td>BIS</td>
<td>Laparoscopic</td>
<td>10</td>
</tr>
<tr>
<td>Cortinez and colleagues</td>
<td>2</td>
<td>NA</td>
<td>Remifentanil TCI</td>
<td>No</td>
<td>BIS</td>
<td>NA</td>
<td>19</td>
</tr>
<tr>
<td>van Kralingen and colleagues</td>
<td>200 or 350 mg bolus</td>
<td>NA</td>
<td>Fentanyl bolus</td>
<td>NA</td>
<td>BIS</td>
<td>NA</td>
<td>20</td>
</tr>
<tr>
<td>Meyhoff and colleagues</td>
<td>2</td>
<td>5.9</td>
<td>0.5 µg kg min</td>
<td>0.43</td>
<td>CSM</td>
<td>Laparotomy</td>
<td>19</td>
</tr>
<tr>
<td>Albertin and colleagues</td>
<td>6.1 (1.8)</td>
<td>6.1 (1.8)</td>
<td>0.15 (0.07)</td>
<td>BIS</td>
<td>Laparotomy</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Pandazi and colleagues</td>
<td>2–3</td>
<td>NA</td>
<td>Epidural and N₂O</td>
<td>BIS</td>
<td>Laparotomy</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Gaszynski and colleagues</td>
<td>5.8</td>
<td>NA</td>
<td>NA</td>
<td>BIS</td>
<td>Laparotomy</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Gaszynski and colleagues</td>
<td>3.8 (1.0)</td>
<td>0.5</td>
<td>0.34 (0.15)</td>
<td>BIS</td>
<td>Laparotomy</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Servin and colleagues</td>
<td>5.4 (2.0)</td>
<td>Fentanyl and N₂O</td>
<td>No</td>
<td>Laparotomy</td>
<td>8</td>
<td></td>
<td></td>
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</table>

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of our control system as reported previously.20 We have previously shown that our controller provides consistent and stable anaesthesia under a variety of circumstances.20 35 53 However, there are obviously a host of other potential combinations that may also work well and the current study cannot demonstrate that other combinations perform better or worse. The propofol–remifentanil relationship we used is thus one solution to the combination problem, but surely not the only one. It is possible that other combinations could yield different relationships between TBW and IBW in the obese. But the solution we propose, using TBW for propofol and IBW for remifentanil works well and provides a satisfactory anaesthetic.

The continuous titration of the effect by an automated controller is feasible and reliable. It optimizes the titration of short-acting i.v. drugs and has probably the potential to improve care for obese patients. The use of the current automated controller guided by the electro-cortical activity demonstrated that the propofol doses in obese and lean patients were nearly identical when expressed as a function of TBW. In contrast, remifentanil doses were similar when expressed in terms of IBW.

**Authors’ contributions**


**Declaration of interest**

N.L., T.C and Foch Hospital are cofounded of MedSteer, a biomedical company to develop research and development of closed-loop tools.

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Appendix
The controller was implemented using Infusion Toolbox 95 version 4.11 which served as a platform: (i) calculating effect-site concentrations of propofol and remifentanil using the PK population of Schneider and colleagues for propofol and Minto and colleagues for remifentanil; (ii) displaying these calculated effect-site concentration estimates in real time; (iii) providing a user interface that permits entry of patient’s characteristic data (sex, age, weight, and height) and modification of upper and lower limits of drug concentrations; (iv) controlling the propofol and remifentanil infusion pumps (Asena GH, Alaris Medical); and (v) recording BIS, calculated effect-site concentrations.
The controller has a cascade structure including a dual proportional-integral-derivative algorithm and a TCI system for the administration of i.v. anaesthetics. The controller uses the parameters from the BIS monitor if the signal quality index is >50%. The controller measures the electromyographic activity, the percentage of burst suppression ratio, and calculates the BIS\textsubscript{error} or the difference between the set point of 50 and the actual measured BIS value. If the BIS\textsubscript{error} is different from 0, the controller determines a new propofol concentration, remifentanil concentration, or both. If the signal quality index is <50, the propofol or remifentanil targets are not modified until the signal quality index is >50.

The controller increases or decreases the drug concentration according to the BIS\textsubscript{error} sign. The error size determines which drug will be modified: if the BIS\textsubscript{error} is small, only the remifentanil is changed; if the BIS\textsubscript{error} is higher than a threshold, the two drug concentrations are changed. The minimal interval between two consecutive controls is set equal to the time to peak effect of each drug; this time interval is shorter for remifentanil\(^{10}\) than for propofol,\(^6\) thus, remifentanil modifications are made more frequently. The feed-forward term gives the rate of change in the error and amplifies the correction of the drugs every 5 s when a measured BIS value is >60. The interaction rule between propofol and remifentanil is as follows: if the controller successively increases the remifentanil concentration more than three times, then the propofol concentration is increased.

A detailed description of the controller has been provided in a previous controlled study.\(^{20}\) In the current study, the controller was identical for the thresholds, rules, propofol gain constants, lower and upper limits of propofol (1.3 and 5 \(\mu\text{g} \text{ml}^{-1}\)), or remifentanil (2 and 12 ng ml\(^{-1}\)) of the previous controller. Throughout the procedure, the investigator could adjust the lower limits of propofol–remifentanil when the BIS decreased to and remained under 40.

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