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A comparison of two techniques for induction of anaesthesia with target-controlled infusion of propofol

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Summary

Induction of anaesthesia with target-controlled infusion of propofol may be achieved by stepwise increases in effect-site concentration until the patient loses consciousness (titration method), or by setting a high effect-site concentration target and observing the calculated effect-site concentration at loss of consciousness (standard method). When the estimated effect-site concentration at loss of consciousness is accurate, the difference between effect-site concentration at loss of consciousness and at recovery of consciousness should be small. This prospective, randomised, controlled trial was designed to compare this difference (effect-site concentration at loss of consciousness – effect-site concentration at recovery of consciousness) associated with the two techniques. Sixty-seven healthy patients undergoing elective hemithyroidectomy were recruited. Induction of anaesthesia was achieved using effect-site target-controlled infusion with the modified Marsh model and k\(_{e0}\) of 1.2 min\(^{-1}\). The median (IQR [range]) difference between effect-site concentration at loss of consciousness and recovery of consciousness was significantly lower in patients in the titration group at 1.2 (0.8–1.5 [0.1–2.9]) µg.ml\(^{-1}\) compared with the standard group 2.1 (1.9–2.6 [0.2–3.6] µg.ml\(^{-1}\); \(p < 0.0001\)). There was a positive correlation between effect-site concentration at loss of, and recovery of, consciousness (\(R = 0.41, p = 0.016\)) in the titration group, which was not seen in the standard group (\(R = -0.15, p = 0.44\)). In conclusion, using the modified Marsh pharmacokinetic model, the titration method for target-controlled infusion propofol at induction of anaesthesia allows closer matching of propofol concentration to depth of anaesthesia than the standard method.

Introduction

There is high interindividual variability in the effect-site concentrations of propofol that result in the loss of consciousness, with levels ranging from 1.5 to 5 µg.ml\(^{-1}\) in both healthy volunteers and surgical patients [1–5]. Consequently, it is not possible to accurately administer propofol based on data from an average population, and titration to clinical response is more appropriate [5].

Target-controlled infusion (TCI) of propofol may be used with either plasma- or effect-site targeting. Since the plasma is not the site of action of propofol, targeting the effect-site is more logical and clinically useful.

Anaesthetic induction using TCI may be achieved by upwards titration, with stepwise increases in effect-site target until the patient loses consciousness. Alternatively, it may be achieved by setting a higher effect-site concentration target and observing the calculated effect-site concentration at loss of consciousness (standard method).
concentration target than is likely to be required, and then observing the calculated effect-site concentration at loss of consciousness [5, 6]. In the rest of this manuscript, the first method of induction will be referred to as ‘titration’ and the second method as ‘standard’.

Previous investigation has shown that there was better correlation between the effect-site concentration at loss of and recovery of consciousness when using TCI with a modified Marsh model and fast effect-site elimination rate constant (k̇e0) of 1.2 ml⁻¹, compared with a k̇e0 of 0.26 ml⁻¹ [6]. It is quite likely that neither k̇e0 is accurate, as more recent research suggests that the optimal median (95%CI) k̇e0 with the Marsh model is 0.6 (0.37–0.78) min⁻¹ [7, 8]. It is also possible that there is interindividual variability in k̇e0 [7]. Although it is not possible to define the most accurate k̇e0 for any individual patient, effect-site TCI needs a reasonably accurate k̇e0 so that the Ce is correctly reflected during clinical application [9].

There is a fundamental difference between the Marsh models with slow and fast k̇e0. The calculated effect-site concentration with a k̇e0 that is too slow always underpredicts, whereas the calculated effect-site concentration always overpredicts when k̇e0 is too fast, making accurate titration very difficult in both situations [9]. However, titration to loss of consciousness and observation of the effect-site concentration may still be possible using the Marsh effect-site TCI with fast k̇e0 by allowing time for equilibrium to be achieved between the plasma and effect-site concentration; in this case, the real effect-site concentration approaches the calculated effect-site concentration [7].

Our hypothesis was that, by titration to loss of consciousness and allowing time for equilibrium between plasma and effect-site concentration to be achieved, individual effect-site concentration could be observed more accurately, and the difference between effect-site concentration at loss of and recovery of consciousness would be reduced. In addition, the need to adjust the effect-site concentration target during the intra-operative period should be reduced. The primary outcome of this study was the difference between calculated effect-site concentration at loss of consciousness and at recovery of consciousness. The secondary outcome measures were related to anaesthetic stability, including the proportion of time that bispectral index™ (BIS) was outside the range of 40–60, and the number of setting changes to the target effect-site during maintenance of general anaesthesia.

**Methods**

This study was approved by the Local Research Ethics Committee of the University of Hong Kong Shenzhen Hospital, and was conducted between March–July 2016. Adult patients of ASA physical status 1–2 undergoing hemithyroidectomy for non-malignant lesions were recruited after gaining written informed consent. Patients were not recruited if they were ASA physical status ≥ 3; body mass index > 30 kg.m⁻²; had concurrent use of sedatives or medication that might influence the central nervous system; or consumption of > 2 units of alcohol per day. No premedication was used. An intravenous (i.v.) cannula was placed and connected to three-way taps and an antireflux valve. After placement of pulse oximetry, ECG, non-invasive blood pressure and BIS (Medtronic, Minneapolis, MN, USA), and recording baseline measurements, induction of anaesthesia was commenced using effect-site TCI with the modified Marsh model and k̇e0 of 1.2 min⁻¹, delivered using a Base Primea TCI pump (Fresenius Kabi, Brezins, France).

Patients were randomly assigned to either titration or standard groups. A list of randomisation numbers was prepared by a statistician who was not involved in the study. Group assignment was kept in an opaque and sealed envelope that was opened by the attending anaesthetist before induction of anaesthesia. All patients received remifentanil TCI using the Minto model [10], with the effect-site target set at 3 ng.ml⁻¹. For patients in the titration group, the effect-site target of propofol was set at 1 μg.ml⁻¹ with a maximum infusion rate of 1200 ml.h⁻¹. Once the effect-site concentration reached the target and the patient was still awake, the effect-site was increased by 0.5 μg.ml⁻¹. When the patient appeared sleepy or had their eyes closed, the time to increase to the next target was delayed by 30 s. This was intended to allow the effect-site concentration to approach the calculated effect-site concentration, in order to compensate for overprediction of calculated effect-site concentration [11]. Loss of consciousness was checked by an anaesthetic assistant who was blinded to the research protocol. The assistant checked for loss of consciousness every 10 s after the propofol infusion started. Loss of consciousness was defined as lack of response to the command ‘open your eyes’, without touching the patient. Calculated effect-site concentration of propofol and BIS were recorded at loss of consciousness.

For patients in the standard group, the effect-site target of propofol was set at 5 μg.ml⁻¹, with the same infusion rate. As in the titration group, the anaesthetic
Assistant checked for loss of consciousness every 10 s, and at this point recorded the calculated effect-site concentration of propofol and BIS.

After loss of consciousness, atracurium 0.5 mg.kg\(^{-1}\) was given and the effect-site target concentration of remifentanil was increased to 5 ng.ml\(^{-1}\). Controlled ventilation was maintained with a facemask once the patient was apnoeic. Two minutes after administration of atracurium, the trachea was intubated. Remifentanil was then decreased to 2–3 ng.ml\(^{-1}\) while the patient was being prepared for surgery.

The calculated effect-site concentration of propofol observed at loss of consciousness was set as the effect-site target for maintenance of anaesthesia. The effect-site target of propofol was adjusted to maintain BIS between 40 and 60 during the surgical procedure. If the BIS was < 40 or > 60, the attending anaesthetist decreased or increased the target effect-site concentration by 0.2–0.5 µg.ml\(^{-1}\). The effect-site target of remifentanil was adjusted according to surgical stimulation. Intravenous morphine 0.1–0.2 mg.kg\(^{-1}\) and dexamethasone 4 mg were given before skin incision, and parecoxib 40 mg or flurbiprofen 50 mg and ondansetron 4 mg were given before completion of surgery.

Target-controlled infusion propofol was stopped 5 min before anticipated completion of skin closure, and remifentanil was stopped upon completion of surgery. If necessary, neuromuscular blockade was reversed with neostigmine and atropine. Recovery of consciousness was defined as a positive response to verbal commands of eye and mouth opening. Tracheal extubation was performed when spontaneous breathing and full consciousness had resumed.

Data collection included calculated effect-site concentration at loss of and recovery of consciousness, number of setting changes for TCI propofol, proportion of time when BIS was < 40 or > 60 and frequency of hypotension, defined as a decrease in systolic blood pressure > 30% baseline. In a pilot study of 11 patients who were induced with the standard method, the mean (SD) difference of calculated effect-site concentration at loss of and recovery of consciousness was 2.1 (0.6) µg.ml\(^{-1}\). Thirty-one patients per group were required to detect a 0.5 µg.ml\(^{-1}\) decrease in difference between effect-site concentration at loss of consciousness and recovery of consciousness, with a power of 90% at the 0.05 significance level.

The primary outcome was compared using the Mann–Whitney U-test. Correlation of effect-site concentration at loss of and recovery of consciousness were compared using Spearman’s correlation analysis. A value of p < 0.05 was considered significant. Data were analysed using SPSS (version 21.0; SPSS Inc., Chicago, IL, USA).

Results

The CONSORT flow diagram for the study is shown in Fig. 1. Two patients allocated to the standard method were induced with the titration method by mistake, and their results were included in the latter group for analysis. Baseline characteristics of the patients are shown in Table 1.

The median (IQR [range]) difference between the calculated effect-site concentration of propofol at loss of consciousness and at recovery of consciousness was significantly lower in patients who were induced with the titration induction method at 1.2 (0.8–1.5 [0.1–2.9]) µg.ml\(^{-1}\), vs. 2.1 (1.9–2.6 [0.2–3.6]) µg.ml\(^{-1}\) with the standard method (p < 0.0001).

Secondary outcome results are given in Table 2. Induction of anaesthesia with the titration method was associated with significantly lower effect-site concentration at loss of consciousness than the standard method, but the effect-site concentration at recovery of consciousness was not different between the two groups. The time to induction was longer using titration, and a lower overall propofol dose for the procedure was used. The number of setting changes was lower when patients were induced with the titration compared with the standard method. When the titration method was used, there was a positive correlation of effect-site concentration at loss of and recovery of consciousness (R = 0.41, p = 0.016), which was not seen with the standard method (R = −0.15, p = 0.44; Fig. 2). Two patients induced with the standard method required phenylephrine to treat hypotension.

The BIS index at loss of consciousness was significantly higher when patients were induced with the titration method, but was not different at the time of intubation and recovery of consciousness (Table 2). The individual BIS profiles from induction to the end of propofol infusion are illustrated in Fig. 3. The proportion of time that BIS was > 60 was significantly higher when patients were induced with the titration method (5.1 [0–11.9 [0–37.5]%] vs. 0 [0–0 [0–23.5]%]; p = 0.033). The proportion of time that BIS was < 40 was significantly lower when patients were induced with the titration method (5.1 [0–11.8 [0–20.0]%] vs. 25.0 (14.7–30.4 [0–60.9]%); p < 0.0001).

The individual profiles of effect-site concentration of propofol are shown in Fig. 4. During a routine visit the day after surgery to check the quality of recovery, no patient had any recall of intra-operative awareness.


**Discussion**

Although we have information on the effect-site concentration of propofol that produces unconsciousness in 50% of subjects (EC50) [2, 3], there is wide interindividual variation. The use of TCI with titration allows personalisation of propofol dosing. The end-point of titration at induction is loss of consciousness, defined by loss of response to verbal command or tactile stimulation. Such titration is not feasible when using volatile anaesthesia, which is usually guided by the standard value for minimum alveolar concentration, despite also showing significant interindividual variability [12]. Hence, the ability to titrate accurately individual propofol requirements with TCI is an important advantage in total intravenous anaesthesia.

Titration and estimation of propofol requirements in individual patients may be particularly important when a depth of anaesthesia monitor is not used, although these monitors also show distinct interindividual variability [13]. Nevertheless, the method of induction can affect the accuracy of the effect-site concentration of propofol at loss of consciousness. This study suggests that by using the titration method, and starting from a low effect-site concentration, overestimation of effect-site concentration is avoided. Also, interestingly, effect-site concentration at loss of consciousness correlates with that at recovery of consciousness only when the titration method of induction is used. This probably indicates that the calculated effect-site concentration with the titration method is more reflective of the effect-site concentration at loss of consciousness. The difference in calculated effect-site

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**Figure 1** CONSORT flow diagram. BIS, bispectral index; TCI, target-controlled infusion.

**Table 1** Characteristics of patients receiving induction of anaesthesia with titration and standard techniques. Values are mean (SD) or number.

<table>
<thead>
<tr>
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<th>Titration</th>
<th>Standard</th>
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<tr>
<td>Age; years</td>
<td>43.8 (12.1)</td>
<td>43.0 (13.1)</td>
</tr>
<tr>
<td>Weight; kg</td>
<td>61.7 (10.4)</td>
<td>58.5 (8.0)</td>
</tr>
<tr>
<td>Sex; female</td>
<td>25</td>
<td>27</td>
</tr>
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Table 2  Secondary outcomes for patients receiving induction of anaesthesia with titration and standard techniques. Values are median (IQR [range]) or number (proportion).

<table>
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<tr>
<th>Outcome</th>
<th>Titration n = 36</th>
<th>Standard n = 31</th>
<th>p value</th>
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<tr>
<td>Effect-site concentration of propofol at loss of consciousness; µg.ml⁻¹</td>
<td>2.7 (2.0–3.0 [1.5–4.0])</td>
<td>3.8 (3.4–4.2 [1.5–5.0])</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Effect-site concentration of propofol at recovery of consciousness; µg.ml⁻¹</td>
<td>1.4 (1.3–1.7 [1.0–2.9])</td>
<td>1.5 (1.3–1.7, [1.1–3.0])</td>
<td>0.332</td>
</tr>
<tr>
<td>Time to induction; min</td>
<td>6.0 (5.0–7.0 [3.0–11.0])</td>
<td>1.0 (1.0–1.0, 0–3.0)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Propofol dose; µg.kg⁻¹.min⁻¹</td>
<td>117.8 (93.7–128.1 [62.2–369.8])</td>
<td>137.7 (115.9–157.8 [56.8–196.1])</td>
<td>0.003</td>
</tr>
<tr>
<td>Remifentanil dose; µg.kg⁻¹.min⁻¹</td>
<td>0.15 (0.13–0.17 [0.09–0.20])</td>
<td>0.17 (0.15–0.19 [0.11–0.30])</td>
<td>0.17</td>
</tr>
<tr>
<td>Number of setting changes</td>
<td>2 (1–3 [0–8])</td>
<td>4 (3–6 [2–8])</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration BIS &lt; 40; %</td>
<td>5.1 (0–11.8 [0–20.0])</td>
<td>25 (14.7–30.4 [0–60.9])</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration BIS &gt; 60; %</td>
<td>5.1 (0–11.9 [0–37.5])</td>
<td>0 (0–0 [0–23.5])</td>
<td>0.03</td>
</tr>
<tr>
<td>BIS at loss of consciousness</td>
<td>75 (70–80 [58–85])</td>
<td>71 (57–77 [40–96])</td>
<td>0.02</td>
</tr>
<tr>
<td>BIS at tracheal intubation</td>
<td>58 (50–63 [40–68])</td>
<td>52 (45–60 [25–73])</td>
<td>0.11</td>
</tr>
<tr>
<td>BIS at recovery of consciousness</td>
<td>76 (71–78 [53–88])</td>
<td>75 (70–78 [56–87])</td>
<td>0.76</td>
</tr>
<tr>
<td>Effect-site concentration of propofol at intubation; µg.ml⁻¹</td>
<td>3 (2.3–3.0 [1.5–4.0])</td>
<td>4 (3.5–4.7 [2.9–5.6])</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Effect-site concentration of remifentanil at intubation; µg.ml⁻¹</td>
<td>5.0 (4.6–5.0 [3.0–5.0])</td>
<td>5.0 (4.3–5.0 [3.0–6.0])</td>
<td>0.95</td>
</tr>
<tr>
<td>Time to wake up after cessation of propofol infusion; min</td>
<td>6.5 (5.0–8.0 [2.0–13.0])</td>
<td>7.0 (6.0–9.5 [0.0–13.0])</td>
<td>0.61</td>
</tr>
<tr>
<td>Time to extubation after cessation of propofol infusion; min</td>
<td>8.0 (7.0–11.0 [5.0–16.0])</td>
<td>9.0 (7.0–11.0 [4.0–13.0])</td>
<td>0.59</td>
</tr>
<tr>
<td>Duration of anaesthesia until extubation; min</td>
<td>102.5 (88.5–119.8 [58.0–79.0])</td>
<td>89.0 (73.5–104.0 [57.0–135.0])</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypotension</td>
<td>11 (30.6%)</td>
<td>11 (35.5%)</td>
<td>0.87</td>
</tr>
</tbody>
</table>
concentration at loss of and recovery of consciousness was larger than expected. This difference could be secondary to hysteresis [14] or study artefact [15]. It is also possible that equilibrium between plasma and effect-site propofol concentrations was not achieved. A previous study suggested that the median (95%CI) apparent $k_{e0}$ of propofol is 0.61 (0.37–0.78) min$^{-1}$ [7] and, consequently, the faster modified Marsh model $k_{e0}$ is likely to have contributed to an overestimation of effect-site concentration. Nevertheless, it is probable that there is inter-individual variation in $k_{e0}$ values, and using a faster $k_{e0}$ with a longer waiting time may allow the real effect-site concentration to approach the calculated effect-site concentration.

Median BIS at loss of consciousness was 75 and 71 in the titration and standard groups, respectively. These values are above the level of 60 suggested by the manufacturer to equate to anaesthesia, despite the patients not responding to verbal commands. A previous study has demonstrated a similar phenomenon [16]. The effect-site target of propofol at loss of consciousness was maintained following induction and during tracheal intubation, while the effect-site target of remifentanil was increased to 5 ng.ml$^{-1}$ for intubation. Since propofol does not provide analgesia, opioids, such as remifentanil and morphine, are required to attenuate painful stimuli [16]. Interestingly, we have noticed that the BIS would then subsequently fall to $<60$ despite maintaining the same effect-site target. This could reflect the measurement latency of BIS, as well as a longer equilibrium time between plasma and effect-site than the modified Marsh model predicted.

With the standard method of induction, the effect-site target is usually set at a higher-than-expected concentration for loss of consciousness. Although the effect-site concentration may be observed as the patient becomes unconscious, the calculated effect-site concentration is not accurate; it will be higher than the actual

![Figure 2](image-url)  
**Figure 2** The intragroup correlation between the effect-site concentrations of propofol (EC) at loss and recovery of consciousness using (a) the titration (●) and (b) standard (○) method at induction of anaesthesia. There was positive correlation with the titration method ($r^2 = 0.405$, $p = 0.016$), but there was no correlation between the effect-site concentrations at loss and recovery of consciousness with the standard method ($r^2 = -0.15$, $p = 0.44$).

![Figure 3](image-url)  
**Figure 3** Individual BIS profiles for each subject in (a) titration and (b) standard groups. Bold line, average BIS value; horizontal lines, target BIS range.
effect-site concentration when the modified Marsh model is used, and even more so for the Schnider model [11]. Moreover, when loss of consciousness occurs and the effect-site target is adjusted to the value observed at this time, the effect-site concentration will continue to rise even though the plasma concentration starts to fall. For these two reasons the standard method is associated with higher propofol doses and lower BIS in the initial phase of anaesthesia. A slightly longer duration of induction is required with the titration method, but overdose is less likely.

In this investigation, we used the modified Marsh pharmacokinetic model with a fast $k_{e0}$ of 1.2 min$^{-1}$, and our results may not apply to a Marsh model with a different $k_{e0}$, or to other pharmacokinetic models [17]. The choice of pharmacokinetic model will also affect the estimated effect-site concentration [7, 18]. We have shown that using the titration method with the modified Marsh model allows us to observe the effect-site concentration at loss of consciousness, with decreased need to adjust TCI concentrations. The subjects in this study were healthy and relatively young. The pharmacokinetic model works well in this group, but may not apply in elderly patients and in patients with haemodynamic instability. The Marsh model does not make any adjustment for age, and has been shown to underpredict plasma propofol concentrations in the elderly [19]. The use of a remifentanil infusion and other analgesia would also have some effect on propofol requirements and brain electrical activity [16]. Slow titration from a low effect-site concentration, using depth of anaesthesia monitoring and appropriate adjustment in effect-site target, may be more important in elderly patients or those with limited haemodynamic reserve than in healthy patients.

There are a number of limitations with this study. It was not possible for the anaesthetist to be blinded to group allocation, which could allow bias. We asked our anaesthetic assistants, who were not aware of the study protocol, to assess consciousness in an attempt to minimise this. However, the same anaesthetist was responsible for measuring the calculated effect-site concentration at recovery of consciousness. The duration of the procedure was longer in patients using the titration method (Table 2), although this should not affect the propofol dose as we compared dose rate in $\mu g.kg^{-1}.min^{-1}$ rather than total dose. Using BIS guidance for propofol dosing in both groups might be another limitation, as this could lead to similar propofol dose delivery. However, to date, BIS and similar processed EEG monitors are the best available objective guide to depth of anaesthesia. The BIS index was recorded manually every 5 min.

In conclusion, using the modified Marsh pharmacokinetic model, the titration method for TCI propofol at induction of anaesthesia allows closer matching of propofol concentration to depth of anaesthesia than the standard method.

**Acknowledgements**

This study was approved by the Local Research Ethics Committee of the University of Hong Kong Shenzhen Hospital (IRB [2015] 88) and registered with the Chinese Clinical Trial Registry (ChiCTR-IOD-16010146).

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