Table 1 Characteristics of patients and surgeries. *Sufentanil 1 μg=fentanyl 10 μg. †The duration of anaesthesia effect defined as the duration between the finish of PNBs to the time the patient felt pain in the operation site. PNB, peripheral nerve block

	Operations (*n*=57)
Sex (male), *n* (%)	30 (52.6)
Age (yr)	50.8 (16–81)
BMI (kg m^{-2})	23.0 (3.5)
ASA physical status, *n* (%)	
1	37 (64.9)
2	19 (33.3)
3	1 (1.8)
Emergency, *n* (%)	11 (19.2)
Time from finish of PNBs to start of surgery (min)	26.2 (17.2)
Type of surgery, *n* (%)	
Open reduction and internal fixation of fractures	10 (17.5)
Removal of internal fixation	10 (17.5)
Deep wound debridement and suture	37 (64.9)
Site of surgery, *n* (%)	
Patella and leg	35 (61.4)
Foot and ankle	22 (38.6)
Duration of surgery (min)	55.4 (32.9)
Time of surgery, median (range)	1 (1–6)
Total use of fentanyl or equivalent* (μg)	99.4 (69.7)
Dosage of dexmedetomidine (μg)	29.1 (2.9)
Postoperative complications	None
Duration of anaesthesia effect† (h)	16.5 (5.6)

should be considered in future guidelines of regional anaesthetic block techniques for surgical procedures distal to the popliteal region. Nevertheless, although those studies were focused on foot and ankle surgery, over half of the surgical interventions in our study were in the upper leg (up to patella level), proximal to the ankle and foot. Even though the success rate in our study was high, we are cautious about extending the technique for longer-duration surgery, as tourniquet pain and discomfort from long periods in one position can both be problematic for patients.

In conclusion, our experience suggests that adding PFCN block to PNB techniques can improve anaesthesia quality for below-knee surgery. However, because of the natural limitations of our observational study, the small sample size, and many confounders (e.g. various doses of intraoperative opioids and local anaesthetics), a further prospective randomised controlled study is warranted to ascertain the role of PFCN block for below-knee surgery.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Clinical validation of pharmacokinetic and pharmacodynamic models for propofol infusion. Comment on *Br J Anaesth* 2021; 126: 386–94

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Editor—We read with interest the paper by Vellinga and colleagues[1] on validation of a recent propofol pharmacokinetic (PK)/pharmacodynamic (PD) model by Eleveld and colleagues[2] compared with earlier propofol models. The authors analysed arterial blood propofol concentrations and bispectral index (BIS; an electroencephalographic measure of drug effect) data during *effect-site target-controlled infusion* (TCI) in 100 patients.

When TCI is used for titration, we propose that the selected TCI concentration is simply a means to an end, which is to achieve a targeted effect in a patient. When reflecting on the various parameters used to assess the PK performance of a model, we contend that the median absolute prediction error of many models (<30%) pales into insignificance in comparison with the PK range of propofol target effect-site concentrations required for the same effect in different individuals (>400%).[3] We also contend that even if the actual arterial concentrations are biased slightly high or low, there is little clinical consequence if the effect is in the targeted range, provided that the bias is stable over time, that is wobble and divergence are low. We note that divergence was not reported by Vellinga and colleagues.[1]

Although the statistics proposed by Varvel and colleagues[4] are undoubtedly the gold standard for assessment of PK performance of a TCI system, we suggest that they may not be optimal for assessment of PD performance during titration to a specific measure of drug effect. We appreciate that Vellinga and colleagues have modified these statistics for BIS performance calculations; however, we suggest that there is an opportunity to develop better methods to characterise TCI performance with respect to BIS values during the induction, maintenance and emergence phases of anaesthesia, such as those proposed by Soltesz and colleagues.[5] We believe that an important feature of clinical titration to effect is the performance of the TCI system in predicting the time course of the effect-site concentration, particularly during induction and after a change in target concentration. For example we expect that clinicians will notice quite a difference during induction and after a change in target concentration when comparing the model by Schnider and colleagues[6,7] with the model by Eleveld and colleagues[2] in non-obese adults because of their very different effect-site equilibration half-times (1.5 *vs* 4.75 min, respectively). Specifically, after the initial induction bolus, a TCI system using the Eleveld model will stop drug administration for *minutes* longer than one using the Schnider model. We note that Vellinga and colleagues did not assess PK/PD performance within 3–5 min after a change in target concentration.

We recently described a correlation of more drug with less effect in clinical data, a phenomenon that we have termed the *drug titration paradox*.[8] This drug titration paradox is also apparent in Figure 4c of Vellinga and colleagues.[1] There is a strong negative correlation between TCI concentration and BIS value, that is lower BIS values between 20 and 40 (i.e. greater effect) correlate with propofol concentrations below 100% Ce50, and higher BIS values between 60 and 80 (i.e. lesser effect) correlate with propofol concentrations above 100% Ce50. Based upon our understanding of the drug titration paradox, we suggest that within the time frame of the study, titration to the desired effect may have been incomplete, and may require a greater range of target concentrations than reported (both higher and lower) to achieve the desired target BIS range of 40–60 in all patients (Fig. 1).

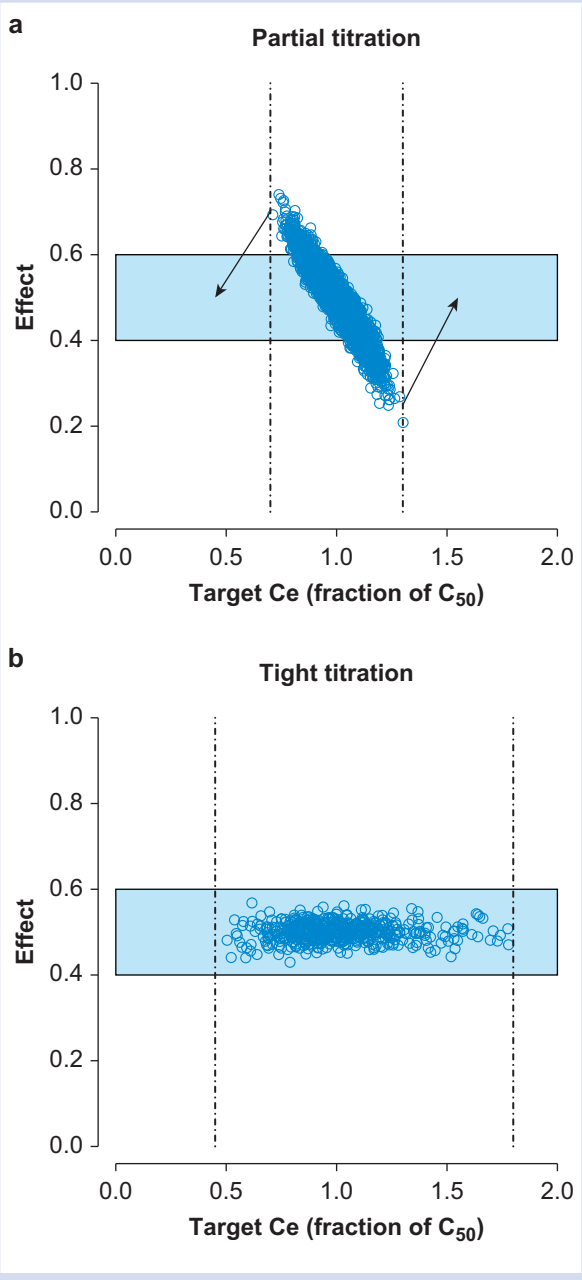

Fig 1. Simulated effect *vs* effect-site concentration (Ce, scaled to Ce50). Each point represents one measurement in one individual during titration to effect (minimum effect = 0, maximum effect = 1) with effect-site target-controlled infusion (TCI). The arrows represent the direction of the shift of individual data points as titration progresses from a to b. (a) Partial titration: relatively narrower range of Ce (dotted vertical lines) with many effects outside the desired effect range of 0.4–0.6. (b) Perfect titration: relatively wider range of Ce (dotted vertical lines) with all effects within the desired effect range of 0.4–0.6.

We acknowledge the time and effort Eleveld and colleagues have invested to develop a propofol PK/PD model for use in TCI across a broad clinical range (children and adults, including older and obese individuals), and that their PK/PD model is

already available from some TCI pump manufacturers for clinical use. However, we believe that there is still more work to be done to validate and compare these different models clinically when they are used for titration to a specific effect, before we discard older models for one 'ultimate' model,[9] particularly if a model developed for a specific subgroup performs significantly better during titration. An alternative approach is to have the pump use the 'best' model for a child, an adult, or an obese adult after the patient covariates have been entered. A potential advantage of this latter approach is that it is easy to accommodate a future model developed for a specific subgroup without requiring yet another analysis of an increasingly larger data set.

We thank Vellinga and colleagues[1] for investigating this important topic and for their contribution to ongoing research into the clinical validation and comparison of different PK/PD models and their performance during titration to a desired clinical effect using TCI.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Relationship between variations in cardiac output and end-tidal CO_2 after phenylephrine infusion in anaesthetised patients

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Editor—Several studies have highlighted a strong relationship between perioperative hypotension and adverse postoperative outcomes (acute kidney injury, myocardial ischaemia, and stroke).[1] Treatment options most commonly used to manage intraoperative hypotension are volume expansion and vasopressors. Phenylephrine, a pure α-adrenergic receptor agonist with α_1 and α_2 actions, is commonly used in this context with well-known haemodynamic effects on arterial pressure, systemic vascular resistance, and left ventricular afterload. However, the effects of phenylephrine on cardiac output (CO) are variable and remain debated. On the one hand,