Effect site concentration of propofol at induction and recovery of anaesthesia - A correlative dose-response study

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ABSTRACT

Background and Aims: Sound knowledge about effect site concentration (Ce) of propofol aids in smooth induction, maintenance and early recovery. We studied the correlation between Ce of propofol at loss of response to verbal command and recovery concentration using target-controlled infusion (TCI) in Indian patients who underwent spine surgeries. Methods: Ninety patients undergoing spine surgeries were included. Total intravenous anaesthesia (TIVA) technique with TCI for propofol using modified Marsh model was used. Entropy and neuromuscular transmission were used. Ce at induction and recovery and the corresponding state entropy (SE) values were noted. Results: The mean propofol Ce and SE at induction were 2.34 ± 0.24 µg/ml and 52 ± 8, respectively. The mean propofol Ce at recovery was 1.02 ± 0.22 µg/ml and 86.80 ± 2.86, respectively. The Ce at recovery was approximately 50% of the induction value. The correlation coefficient ‘r’ between Ce at induction and recovery was 0.56. The mean infusion dose of propofol during the maintenance period was 81 ± 14.33 µg/kg/min. The average induction dose of propofol was 1.17 ± 0.2 mg/kg. Conclusion: There is a positive correlation between Ce at induction and recovery. Ce for recovery may have to be set at a lower level during TCI-TIVA and appropriately infusion should be stopped for early recovery. The induction and maintenance doses of propofol are lower than the recommended doses. Data emphasise the need for pharmacokinetic model based on our population characteristics.

Key words: Effect site, entropy, pharmacokinetic model, propofol
computer programmed system which works based on the parameters entered.\cite{8} The Ce for induction has been defined, but recovery concentration may vary. The correlation between Ce at induction and recovery will enable to define recovery time and hence facilitate timely cessation of propofol infusion and thus early recovery.

We conducted this study to look for the correlation between Ce of propofol at loss of response to verbal command (Ce IND) and effect site concentration at recovery (Ce REC) using TCI in patients who underwent spine surgeries. Our secondary outcome was to study the induction dose of propofol in the study cohort using TCI, based on the loss of response to verbal command.

**METHODS**

This was a prospective observational study. The study was conducted in a tertiary healthcare institute and was approved by the institutional ethics committee. The study was conducted over a period of 1 year from June 2014 to May 2015. Written informed consent was obtained from all patients. Ninety patients of Indian origin aged between 20 and 60 years with American Society of Anesthesiologists physical status 1 and 2 were scheduled for elective spine surgeries with duration of surgery >2 h were included in the study. Patients allergic to egg preparations and upper cervical spine procedures were excluded from the study.

Apart from basic monitors, which included electrocardiogram, non-invasive blood pressure and oxygen saturation; entropy (GE B850 Monitor Entropy Module, Helsinki, Finland) and neuromuscular transmission (NMT) (Kinemyography Technique-GE B850 Monitor NMT Module, Helsinki, Finland) were monitored. The train of four (TOF) mode of stimulation was used to assess the depth of neuromuscular blockade and recovery. Baseline vital parameters and entropy values were noted. All patients received 2 µg/kg of IV fentanyl 5 min before induction of anaesthesia.

Anaesthesia was induced with TCI device (Injectomat™ total intravenous anaesthesia [TIVA] Agilia, Fresenius Kabi, Germany) using the modified Marsh model. The modified Marsh model uses a faster equilibrium rate constant (K\text{eq}) of 1.2/min than the Marsh model to give a more accurate prediction of Ce.\cite{7,9} Patients were pre-oxygenated and 100% oxygen was continued throughout the induction process. All patients received propofol 1% through a large-bore IV canula. The infusion was started with the initial Ce set at 1.5 µg/ml. The dose was escalated in increments of 0.2 µg/ml till loss of response to a standard verbal command was achieved. The response was assessed after starting the infusion and the concentration at which loss of response occurred was noted. When the dose was escalated in 0.2 µg/ml increments, reassessment was done once the reset Ce was achieved. The sequence was repeated till the loss of response to verbal command occurred. The verbal command here is defined as calling out the patient’s name and the response is to open his/her eyes and loss of response is defined as failure to respond to command, corresponding to the Modified Observer’s Assessment of Alertness/Sedation scale (MOAA/S)\cite{10} of 2 [Table 1]. At this time, the corresponding Ce was noted as Ce IND and state entropy (SE) value as SE IND. The induction dose of propofol was also noted. Neuromuscular blockade was achieved with rocuronium bromide.

Balanced anaesthetic technique with controlled ventilation and neuromuscular blockade was employed. Anaesthesia was maintained with oxygen 50%, nitrous oxide 50% and propofol infusion. Analgesia was achieved with intermittent bolus dose of fentanyl at 1 µg/kg IV during the maintenance period and the last dose was given at the beginning of closure approximately 30–40 min prior to the end of surgery. Ce of propofol was titrated to maintain SE values between 40 and 50 to achieve adequate depth of anaesthesia. Any episode of hypotension during induction and surgery was noted. Nitrous oxide and propofol infusion was stopped and FiO\textsubscript{2} of 1 was administered at the beginning of skin closure. TCI was kept on to note the recovery concentration. Trachea was extubated after achieving a TOF ratio of >0.9. The Ce at recovery (Ce REC) was assessed every 5 s by calling out the patient’s name. Ce REC here is defined as eye opening in response to calling out the patient’s name (MOAA/S of 4). The positive response was confirmed again at

| Response                                           | Score |
|-----------------------------------------------------|-------|
| Agitated                                            | 6     |
| Responds readily to name spoken in normal tone (Alert)| 5     |
| Lethargic response to name spoken in normal tone     | 4     |
| Responds only after name is called loudly and/or repeatedly | 3     |
| Responds only after mild prodding or shaking         | 2     |
| Does not respond to mild prodding or shaking         | 1     |
| Does not respond to deep stimulus                    | 0     |

**Table 1: Modified Observer’s Assessment of Alertness/Sedation Scale (MOAA/S)**
the corresponding Ce. The corresponding SE value was noted as SE REC. The time taken from the end of propofol infusion to extubation was also noted.

Assuming power as 90%, alpha error as 5% and standard deviation (SD) based on previous studies,[11,12] the sample size was calculated as 90. The statistical software, namely SPSS version 23.0 (Statistical Package for the Social Sciences, IBM, New York, US, 2015) was used for the analysis of the data. Microsoft Word and Excel were used to generate graphs and tables. Data distribution was normal. Continuous quantitative measures were collected. Pearson’s correlation coefficient, a parametric test, was used to determine the linear relationship between variables. The primary outcome variable was to measure the correlation between the defined study variables. Secondary descriptive and inferential statistical analyses have been carried out in the present study. Results on continuous measurements are presented as mean ± SD (minimum–maximum).

RESULTS

The patients’ demographic characteristics are shown in Table 2. The mean duration of infusion of propofol was 3.8 h. The mean propofol Ce IND and SE IND were 2.34 ± 0.24 µg/ml and 52 ± 8, respectively. The lowest SE at induction was 30. The mean Ce REC and SE REC were 1.02 ± 0.22 µg/ml and 86.80 ± 2.86, respectively [Figure 1]. The correlation coefficient ‘r’ between Ce IND and Ce REC was 0.56 [Figure 2]. The mean infusion dose of propofol and Ce during the maintenance period was 81 ± 14.33 µg/kg/min and 2.37 ± 0.35 µg/ml, respectively. The trend of SE values from the end of propofol infusion till tracheal extubation is shown in Figure 3. SE values and dose of propofol at induction are depicted in Figure 4. No hypotension was observed in any of the patients during induction, maintenance and recovery. The average induction dose of propofol was 1.17 ± 0.2 mg/kg and the mean time from the end of propofol infusion to extubation was 14.8 ± 7.18 min. The average total dose of IV fentanyl administered was 3.5 µg/kg.

| Characteristic | Values          |
|----------------|-----------------|
| Age (year)     | 48.53±11.41     |
| Male:Female    | 51:39           |
| Height (cm)    | 162.05±8        |
| Weight (kg)    | 64.49±12.6      |

DISCUSSION

Target-controlled TIVA offers advantage of titrating to the effect with continuous Ce measurement. The recommended Ce of propofol for maintaining adequate depth of anaesthesia when combined with nitrous oxide or opioid varies from 2.5 to 8 µg/ml. The mean Ce for recovery of consciousness (ROC) is <1.2 µg/ml,
but varies with high opioid use. We did not measure plasma propofol concentration as the modified Marsh model used in our study is widely accepted. However, the various values observed using the model were lower than the recommended dose which could be possibly due to ethnic variations. In our study, with modified Marsh model, the mean propofol Ce IND and Ce REC were 2.34 ± 0.24 and 1.02 ± 0.22 µg/ml, respectively. The correlation coefficient between Ce at induction and at recovery was 0.56. Fentanyl has its effect on Ce of propofol both at induction and recovery and hence the observed values are standardised. Figure 2 suggests that Ce REC is approximately 50% of the value of Ce IND and hence majority of patients could be expected to recover at 50% of the induction value. Studies have shown the effect of various clinical variables on Ce REC.

Various factors explain the variation between Ce IND and Ce REC. One such factor is hysteresis. There is a time lapse of approximately 2 min for equilibration between plasma and effect site. Hence, induction could have occurred at a concentration lower than the one which was actually measured. Although the pharmacokinetic models incorporated into the TCI devices have been designed to nullify the hysteresis effect, it may not be completely false proof.

Other possible explanations are the process of change from awake to anaesthetised state and the vice versa are highlighted by phase transition models. The models show that the cortical neurons change from normal levels to a hypoactive firing state when unconsciousness ensues with anaesthesia, but as an aberrant switch mechanism. The recovery from anaesthesia could be explained as the reverse of the mechanism mentioned above. However, more interestingly, the critical points for loss of consciousness (LOC) and ROC are different. It could be so because the probability of moving in one direction need not be the same as the probability of moving in the opposite direction. Hence, the patient might recover at a lower concentration of an anaesthetic than that required for anaesthetic induction. Other parameters such as age, gender, BMI and opioid administration may influence the Ce. We have postulated the results based on modified Marsh model which takes only weight for calculation. Other factors were not considered in the current study.

Besides, prior to induction, there is a paradoxical excitation in brain activity which is referred to as drug’s biphasic effect. This could explain why LOC occurs at higher Ce, as such more dose of propofol is required to overcome the biphasic effect and to act on the entire cortical inhibitory neurons.

Contrary to our results, Iwakiri et al. reported that the Ce at LOC and ROC were similar. However, it was done on volunteers without surgical stimulus and for a duration of 15 min. Shibuta et al. reported that in female patients the Ce at ROC was higher than that at LOC. They defined LOC and ROC based on response to a physical stimulus rather than a verbal command. Hence, a positive response might have been elicited at a higher Ce. Many studies have reported a positive correlation between Ce IND and Ce REC, observed a Ce LOC of 4.4 ± 1.1 µg/ml and Ce ROC of 1.1 ± 0.3 µg/ml and correlation coefficient of 0.23 using Schnider model. Chan et al. reported a positive correlation (r² = 0.28) between Ce LOC and Ce ROC in their retrospective study. The correlation coefficient in our study was 0.56.

The average time to stop the infusion before the end of surgery and the expected time for ROC could possibly be determined from our observation. Our results give an approximate prediction of Ce REC. Thus, when using TCI-TIVA technique, the Ce REC can be set at 50% of the induction concentration required and accordingly infusion can be stopped to facilitate an awake patient at extubation. We also observed that the average induction dose of propofol after fentanyl bolus in our patients was much lower (1.17 mg/kg) than the recommended dose of 2-3 mg/kg as per literature. Our results are supported by Puri et al. who observed a lower volume of distribution and clearance of propofol in young healthy Indian volunteers. Despite the lower induction dose in our study, the Ce observed was 2.34 ± 0.22 µg/ml and the entropy values correlated with the hypnotic range. The average maintenance dose of propofol was 81 ± 14.33 µg/kg/min along with fentanyl, which is
lower than the recommended dose during balanced anaesthesia. This is explained by the ethnic variation in pharmacokinetics and pharmacodynamics observed following propofol administration. A study done by Puri et al.\textsuperscript{(25)} in Indian patients who underwent major surgical procedures showed a lower induction dose of propofol of 1.4 mg/kg using closed loop anaesthesia delivery system and our results are similar to their findings. Puri et al.\textsuperscript{(26)} in their study observed an effective concentration (EC\textsubscript{90}) and EC\textsubscript{95} of plasma propofol as 2.3 µg/ml and 2.8 µg/ml, respectively, for loss of response to verbal command without fentanyl in patients who went through elective surgeries. The data give supportive evidence on propofol pharmacokinetics in Indian patients.

There are certain limitations in our study. We did not take into account the factors such as age, gender and BMI in the current study which might influence the Ce of propofol at induction and recovery. Besides, we escalated the Ce of propofol based on clinical response rather than a fixed time interval; the latter being a better method for accurate estimation of Ce IND and propofol dosage.

The results from our observation can be a guide to set Ce for induction and also to predict the Ce for recovery and thus the duration required for recovery after the end of propofol infusion when using modified Marsh model-based TCI-TIVA. The pharmacokinetic models in modern TCI are based on data from Western population. Hence, there is a need for pharmacokinetic models in TCI based on the characteristics of the Indian population.

**CONCLUSION**

From our observation, we conclude that there is a mild positive correlation with respect to Ce at induction and recovery. Ce REC is lower than Ce IND and it has got multifactorial explanations. The induction dose of propofol and its infusion dose for maintenance in our population were lower than the recommended dose. The Ce for recovery may have to be set at half the induction value during TCI-TIVA and appropriately infusion should be stopped for early recovery.

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**Conflicts of interest**

There are no conflicts of interest.

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