Original Article

Estimation of median effective effect-site concentration (EC50) during target-controlled infusion of propofol for dilatation and curettage – A prospective observational study

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ABSTRACT

Background and Aims: Propofol is the drug of choice for sedation in daycare procedures due to its pharmacokinetic properties. Propofol delivery using target-controlled infusion (TCI) pump reduces adverse effects like hypotension and apnoea. In this study, we estimated the median effective effect-site concentration of propofol in patients undergoing dilatation and curettage. **Methods:** Patients of the American Society of Anesthesiologists physical status class I–III, aged 40–70 years, undergoing elective dilatation and curettage were recruited for the study. All patients received 1 µg/kg fentanyl and 20 mg lignocaine. The first patient received an effect-site concentration of propofol at 4 µg/mL with TCI Schneider pharmacokinetic model. Failure was defined as patient movement at any time during the procedure. According to the 'BiasedCoin Design' up-and-down sequential method, the response of the previous patient determined the effect-site concentration of propofol of the next patient. The study was terminated once forty patients completed the procedures successfully. Probit analysis was used to determine EC50. **Results:** Fifty-three patients were recruited for the study. The various effect-site concentrations of propofol EC50, EC90, and EC95 in providing sedation for dilatation and curettage were 3.38 µg/mL, 4.29 µg/mL, and 4.60 µg/mL, respectively. The incidence of hypotension and apnoea were comparable among the various concentrations of propofol. The mean duration of the propofol infusion was 20 ± 2.86 min. The time to recovery from propofol sedation was 6.97 ± 1.76 min. **Conclusion:** A median effective effect-site concentration of 3.38 µg/mL of propofol is required to prevent patient movement during uterine dilatation and curettage.

Key words: Dilatation and curettage, infusion pumps, propofol

INTRODUCTION

Dilatation and curettage is a commonly performed daycare gynaecological procedure in elderly patients. Cervical biopsy and cervical curettage are associated with visual analogue scale (VAS) pain scores ranging from four to six on a 10-point scale.[1] Previously, various diagnostic and therapeutic procedures were done under local anaesthesia. Sedation has become the standard of care for these procedures in recent times.[2] Propofol is the drug of choice for sedation in daycare procedures due to its pharmacokinetic properties.[2-4] The recommended intravenous bolus dose of propofol at 2.5 mg/kg could be associated with significant cardiovascular and respiratory depression.[5,6] Elderly women are more prone to

cardiovascular and respiratory depression when propofol is given as a bolus. The difficult airway in them necessitates avoidance of apnoea caused by propofol bolus dose.[7] Propofol given as infusion prevents these two complications. Hence, several manual infusion regimens were put forth to reduce the dose requirement and ensure rapid emergence, but their use was limited by the inaccurate prediction of propofol effect-site concentrations. Target controlled infusion (TCI), refers to a system by which a drug is given intravenously with a pump controlled by a computer; the Schneider model aims to get a target effect-site concentration chosen by the user.[8] There is no literature evidence mentioning the median effective effect-site concentration of propofol in patients undergoing dilatation and curettage to guide anaesthesiologists during propofol TCI. Hence, this study was designed to determine the median effective effect-site concentration during target-controlled infusion of propofol with fentanyl as an adjuvant in patients undergoing dilatation and curettage.

METHODS

This prospective observational study was conducted from May 2019 to June 2020. The study was approved by the Institutional Research Committee and Institutional Human Ethics committee and registered with the Clinical Trials Registry of India (CTRI/2019/05/019151). After obtaining written informed consent, the patients undergoing elective cervical dilatation and curettage formed the study population and were recruited by continuous sampling method. Inclusion criteria were patients of the American Society of Anesthesiologists (ASA) physical class I and II and 40–70 years of age. Patients with allergy to study drugs, difficult airway, risk of aspiration, obesity [body mass index (BMI) > 35], and reactive airway were excluded. After standard preanaesthetic examination, patients fulfilling study criteria were recruited for the study, and written informed consent was obtained from each patient. The patients were advised a fasting period of at least 6 h, and aspiration prophylaxis was given. Sedative premedication was avoided in all the patients.

In the pre-anaesthetic room, a 20-gauge venous cannula was secured in the left wrist, and the patient was preloaded with Ringer's lactate solution 5 mL/kg. In the operating theatre, standard monitoring of electrocardiogram, oxyhaemoglobin saturation, non-invasive blood pressure monitoring and end-tidal carbon dioxide concentration were done. The patients received oxygen of 2 L/min by nasal prongs, and intravenous injection fentanyl (1 μg/kg) was given 5 min before initiation of propofol infusion.[9] Intravenous lidocaine 20 mg with venous occlusion for 2 min was given to relieve pain due to injection of propofol. All the patients received propofol infusion at an effect-site concentration according to 'Biased Coin Design' up-and-down sequential method using a TCI pump (Injectomat TIVA Agilia V0.1, Fresenius kabi, USA) with Schneider pharmacokinetic model software. The first patient received an effect-site concentration of propofol at 4 μg/mL with TCI Schneider pharmacokinetic model. The response of the previous patient determined the effect-site concentration of propofol of the next patient. If the procedure was a success, then the next patient received either 0.5 μg/mL lower or the same concentration as the previous patient through 'Biased Coin Design' up-and-down sequential method.[10,11] 'Biased Coin Design' up-and-down sequential method is like tossing a coin. If the head came when we tossed a coin, the next patient received the same concentration as the previous patient; in the case of a tail, the next patient received 0.5 μg/mL lower than the previous patient. If there was a patient movement, then the next patient received 0.5 μg/mL higher than the previous patient. The patients were positioned for the surgical procedure 1 min after achieving the set effect-site concentration. Patient movement at any time during the procedure was considered a failure, and the surgical step during that time was noted. Movement was defined as a gross movement of any part of the body, straining or making noise. If there was patient movement, further course of anaesthesia maintenance was decided by the attending anaesthesiologist either by giving a bolus of propofol or increasing the effect-site concentration.

Fall in systolic blood pressure less than 90 mmHg was treated with a fluid bolus of 100 mL and bradycardia with injection atropine 0.3 mg intravenously. Upper airway obstruction or apnoea was managed with assisted ventilation using a closed circuit.

Statistical Package for Social Sciences for Mac 21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The sample size was calculated from a previous study as 40 successful procedures, based on 'Biased Coin Design' up-and-down

sequential method.[12] The median effective effect-site concentration (EC50) of propofol which enables successful uterine dilatation and curettage was determined by Probit analysis. Chi-square test was used for the categorical variables like the incidence of hypotension, apnoea, bradycardia.

RESULTS

Fifty-three patients were recruited for the study [Figure 1]. The mean age and BMI were 47 (45–49) years and 25 (24–26) kg/m², respectively. The number of patients having successful procedures for each effect-site concentration is represented as a ratio (percentage) [Table 1]. The 'Biased Coin Design' up-and-down sequence in successive patients was noted [Figure 2]. The effect-site concentration of propofol EC50, EC90 and EC95 was 3.38 µg/mL, 4.29 µg/mL and 4.60 µg/mL, respectively in providing sedation for dilatation and curettage. The incidence of hypotension and apnoea were comparable among the various concentrations of propofol [Table 2], and none of the patients developed bradycardia. However, hypotension was treated with 50–100 mL of intravenous fluid and the apnoea by simple stimuli like head-tilt or jaw thrust and none of the patients required vasopressor or bag and mask ventilation. Out of 53 patients, 13 patients had movements with

Table 1: Number of successful procedures for various effect-site concentrations of Propofol	
Effect-site concentration µg/mL (*n*)	Success/failure ratio (percentage)
3.0 (3)	1/2 (33%)
3.5 (15)	7/8 (47%)
4.0 (25)	24/1 (96%)
4.5 (6)	4/2 (66%)
5.0 (4)	4/0 (100%)

Values are expressed as a ratio (percentage

Table 2: The incidence of hypotension and apnoea for various effect-site concentrations of Propofol		
Effect-site concentration µg/mL (*n*)	Hypotension yes/ no (percentage)	Apnoea yes/ no (percentage)
3.0 (3)	0/3 (0%)	0/3 (33%)
3.5 (15)	1/14 (6%)	2/13 (13%)
4.0 (25)	6/19 (24%)	2/23 (8%)
4.5 (6)	0/6 (0%)	1/5 (16%)
5.0 (4)	1/3 (33%)	1/3 (33%)
P	0.369	0.803

Values are expressed as a ratio (percentage). The statistical test used was the Chi-square test
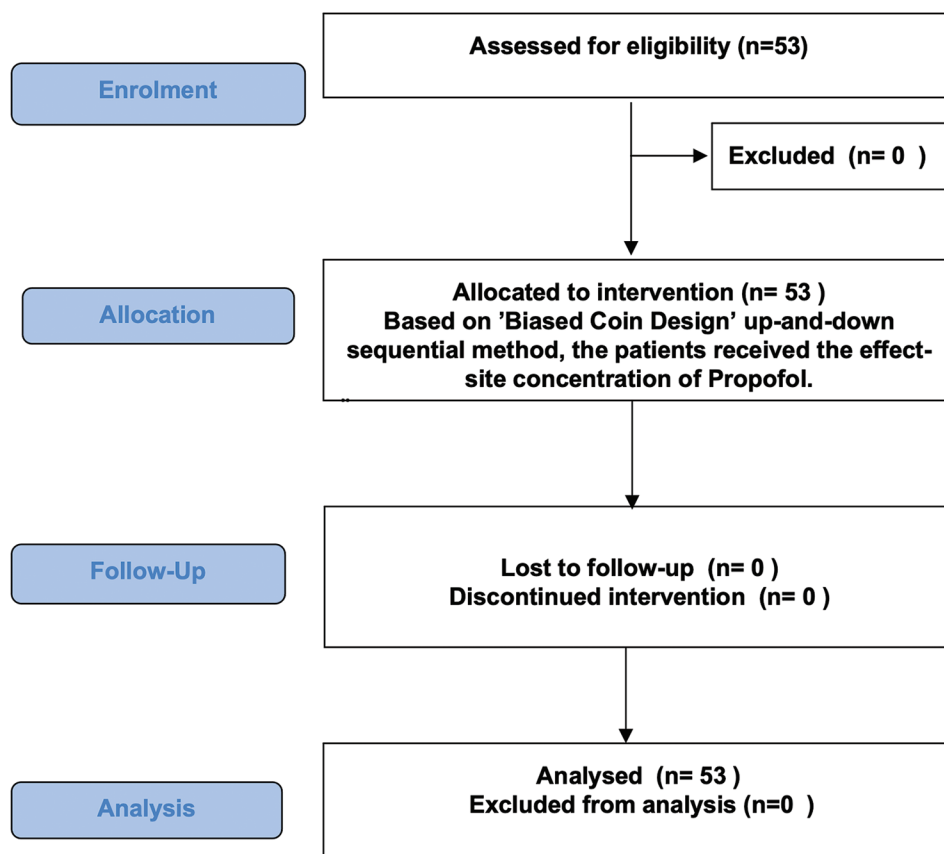

Figure 1: Strengthening the reporting of observational studies in Epidemiology (STROBE) Flow chart
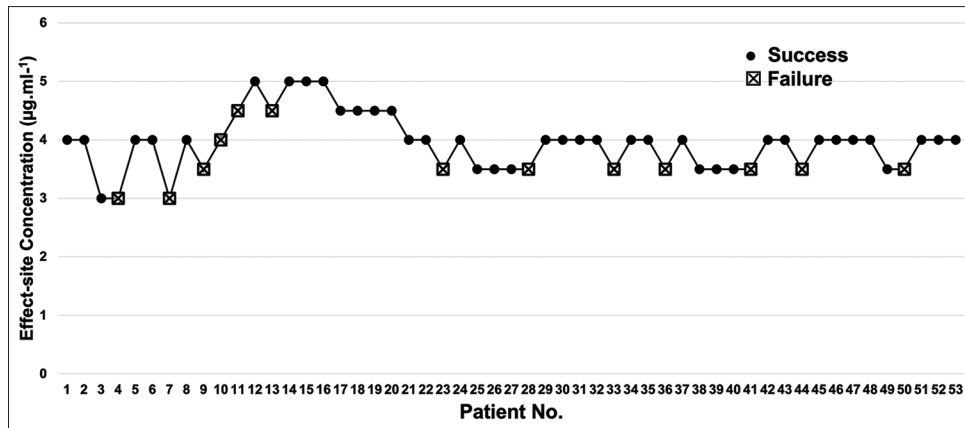
Figure 2: The line shows the effect-site concentration of propofol in successive patients, and the marker depicts the outcome. Success (black circles); Failure (black cross)

various effect-site concentrations of propofol. The surgical step at which movement occurred was noted. The movements were observed while the surgeon was holding the cervix with a vulsellum in nine patients, and four patients had movement during cervical dilatation. The mean duration of the propofol infusion was 20 ± 2.86 min (mean ± standard deviation). Time to recovery from propofol sedation was 6.97 ± 1.76 min (mean ± standard deviation). The fastest recovery was seen in 3 min, and the slowest recovery was seen in 12 min.

DISCUSSION

Procedural sedation with propofol has higher patient satisfaction and diagnostic yield, shorter time to sedate as well as recovery.[2,13] These advantages make physicians prefer propofol sedation compared to other sedative techniques or no sedation in various short outpatient-based diagnostic and therapeutic procedures.[13–16] Being cost-effective with comparable complication rates, TCI or computer-assisted personalised sedation regimens are recommended techniques for non-anaesthesiologist administering sedation using propofol.[17] Hence, the EC50 of propofol for various diagnostic procedures can help us to provide safe sedation. The increase in the incidence of uterine malignancy and the dependability of treatment on the histopathological diagnosis mandates uterine dilatation and curettage procedure to have a high diagnostic yield.

In this study, we evaluated the median effect-site concentration for sedation during uterine dilatation and curettage. We believe that this is the first study evaluating propofol EC50 using Schneider effect-site concentration model for dilatation and curettage. We found that the effect-site concentration of propofol EC50 and EC90 in providing sedation for dilatation and curettage was 3.38 µg/mL and 4.29 µg/mL, respectively. Darlong *et al.*[9] showed that administration of fentanyl 5 min prior to propofol administration caused a marked reduction in the propofol dose. This reduction of propofol requirement leads to a significant reduction in the incidence of hypotension. Hence, we administered fentanyl 5 min prior to propofol infusion in our study.

Li *et al.*[15] studied the pharmacodynamic interaction between fentanyl and propofol when used in combination and determined the EC50 of propofol required for colonoscopy in elderly patients which was 3.08 µg/mL. EC50 of propofol for uterine dilatation and curettage (3.38) was higher compared to EC 50 of propofol for colonoscopy. This may be due to the differences between the studies; firstly, the invasiveness of uterine dilatation and curettage is high compared to colonoscopy and secondly, the Marsh model used in their study compared to the Schneider model in our study.

The age range of our study group was 40–67 years. Kazama *et al.*[18] had designed a study to determine the plasma propofol concentrations at which somatic or gag responses to insertion of gastroscope are suppressed in 50% of the patients. Younger (17–49 years) age group required higher EC 50 of propofol (2.23µg/mL) compared to 1.75 µg/mL (50–69 years.) and 1.40 µg/mL (70–89 years). For all age groups, the propofol EC50 requirement for gastroscopy was less than for dilatation and curettage. This could be attributed to the fact that the invasiveness of uterine dilatation and curettage is high compared to colonoscopy

The surgical step at which movement occurred was noted in our study. During dilatation and curettage, there are three painful steps viz-holding cervix with vulsellum, cervical dilatation, and uterine curettage. The first movements were observed while the surgeon was holding the cervix with a vulsellum in nine patients and four patients had movement during cervical dilatation. These patients were considered a failure, and further patient management depended on the anaesthesiologist's choice.

The incidences of hypotension and apnoea were comparable among the various effect-site concentrations of propofol used in this study. Hypotension was encountered in 8/53 patients (15.1%), apnoea was encountered in 6/53 patients (11.3%), and none of the patients had bradycardia. These results were dissimilar to studies done by Hunt-Smith[19] and Russell *et al.*[20] where the incidence of hypotension and apnoea was 69.6% post-induction. Russell *et al.* attributed this higher percentage to the administration of temazepam and injection fentanyl at 1.5 µg/kg. Hypotension was treated with 50–100 mL of intravenous fluid and the apnoea by simple stimuli like head-tilt or jaw thrust, and none of the patients required vasopressor or bag and mask ventilation. The incidence of apnoea was less in effect-site concentration group than in the plasma concentration group (42% vs 85%) as demonstrated by Struys *et al.*[21] In our study, the incidence of hypotension was (8%–33%), and the apnoea was treated by a simple stimulus like head-tilt or jaw thrust and none of the patients required vasopressor or bag and mask ventilation.

Mean time taken for eye-opening spontaneously or on command in our study was 6.97 ± 1.76 min. A study done by Russell *et al.*[20] showed mean time taken was 8.5 ± 6.49 min. This can be attributed to the fact that oral temazepam 20 mg was administered approximately 1 h before induction of anaesthesia. They also administered 1.5 µg per kg of fentanyl, but we administered only 1µg per kg. Nitrous oxide was also not administered in our study.

In a study done by Servin FS *et al.*,[22] induction of anaesthesia with TCI was achieved with less propofol than with manually controlled infusion (1.69 ± 0.5 vs 2.31 ± 0.75 mg/kg), but it took a longer time (71 ± 54 vs 61 ± 31 s). Mean overall propofol administration was somewhat greater with TCI (12.1 ± 5.08 vs 11.0 ± 5.96 mg/kg/h), resulting in a

deeper, more appropriate anaesthetic depth. Hence, we used TCI in our study.

Various sequential and non-sequential designs are described in the literature to determine the ED50 and ED95 along the dose-response curve. Sequential designs are advantageous for the estimation of effective dose with small sample size and outperform non-sequential designs by having smaller mean square error for the same sample size. Dixon up-and-down method is the commonly used design to determine ED50 with the smallest sample size of six.[23] Limitations of this method are that this is not suitable to estimate other quantiles, and the starting dose should be near to the ED50.[24] While ED95 will be the ideal dose that can be practised, 'Biased Coin Design' derived from the up-and-down technique is effective for the estimation of any quantile of the dose-response curve. So, we have chosen 'Biased Coin Design' up-and-down sequential method in this study.[10]

CONCLUSION

Based on the results and the methodology employed, it is concluded that effect-site concentration of propofol (EC50) for providing sedation to dilatation and curettage is 3.38 µg/mL.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest
There are no conflicts of interest.

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