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*Original Article*

# Effects of penehyclidine hydrochloride on the propofol dose requirement and Bispectral Index for loss of consciousness

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**Abstract:** Penehyclidine hydrochloride (PH), a new anticholinerigic drug associated with few cardiovascular side effects, was used widely as premedication in China. There is no information on the pharmacodynamic interaction between PH and anesthetics for loss of consciousness (LOC). This study was designed to determine the effects of premedicated PH on the propofol dose requirement for LOC and Bispectral Index (BIS) during target-controlled infusion (TCI) of propofol. Forty patients were randomly allocated to 1 of 2 groups to receive PH (Group PH) or normal saline (Group NS). TCI propofol was administered 30 min after PH or normal saline was given. During study period, BIS value, mean arterial pressure (MAP), heart rate (HR) and the Observer's Assessment of Alertness/Sedation (OAA/S) rating scale were recorded. Predicted effect-site propofol concentrations (Ce) and the total propofol dose were recorded when end-point was achieved. The time to reach end point was also noted. The time to reach LOC was shorter in Group PH than Group NS ($p < 0.05$). The predicted propofol Ce and consumption based on body weight of each patient were lower in Group PH than Group NS ($p < 0.05$). BIS values were not significantly changed before propofol infusion, and decreased gradually as propofol Ce increased and were not significantly different when LOC was reached between two groups ($p > 0.05$). We conclude that premedicated PH reduces the propofol Ce and dose requirement for LOC, but has no effect on BIS.

**Keywords:** Penehyclidine hydrochloride, propofol, Bispectral Index, target-controlled infusion

## Introduction

Penehyclidine hydrochloride (PH), a new anticholinerigic drug was developed by the Institute of Pharmacology and Toxicology, Academy of Military Medical Sciences in China [1, 2]. PH, selectively blocking $M_1$ and $M_3$ receptors, is a more potent antisialagogue than the others of this class, and has few $M_2$ receptor-associated cardiovascular side effects [3]. In addition to its use to decrease the secretion of salivary gland, PH has greater central nervous system effect that causes sedation and amnesia. So PH is often used as premedication for anesthesia, especially patients with cardiac ischemia.

However, there is no information on the pharmacodynamic interaction between PH and anesthetics for loss of consciousness. Propofol is an intravenous hypnotic agent that is widely used for induction and maintenance of anesthesia. Target-controlled infusion (TCI) is a developed infusion system that maintains particular target plasma-site or effect-site concentration of a drug using standard pharmacokinetic equations [4].

The effect of regular PH premedication on anesthetic requirements has not been studied previously. Therefore, the present study is designed to investigate the effect of PH premedication on the propofol dose requirement at similar depth of anesthesia as assessed by clinical endpoint and the Bispectral Index (BIS) analysis of the electroencephalogram (EEG).

## Methods

The Study was conducted at West China Hospital of Sichuan University, which is a large-scale, (4,300 impatient beds) comprehensive hospital in Chengdu, Sichuan Province, China.

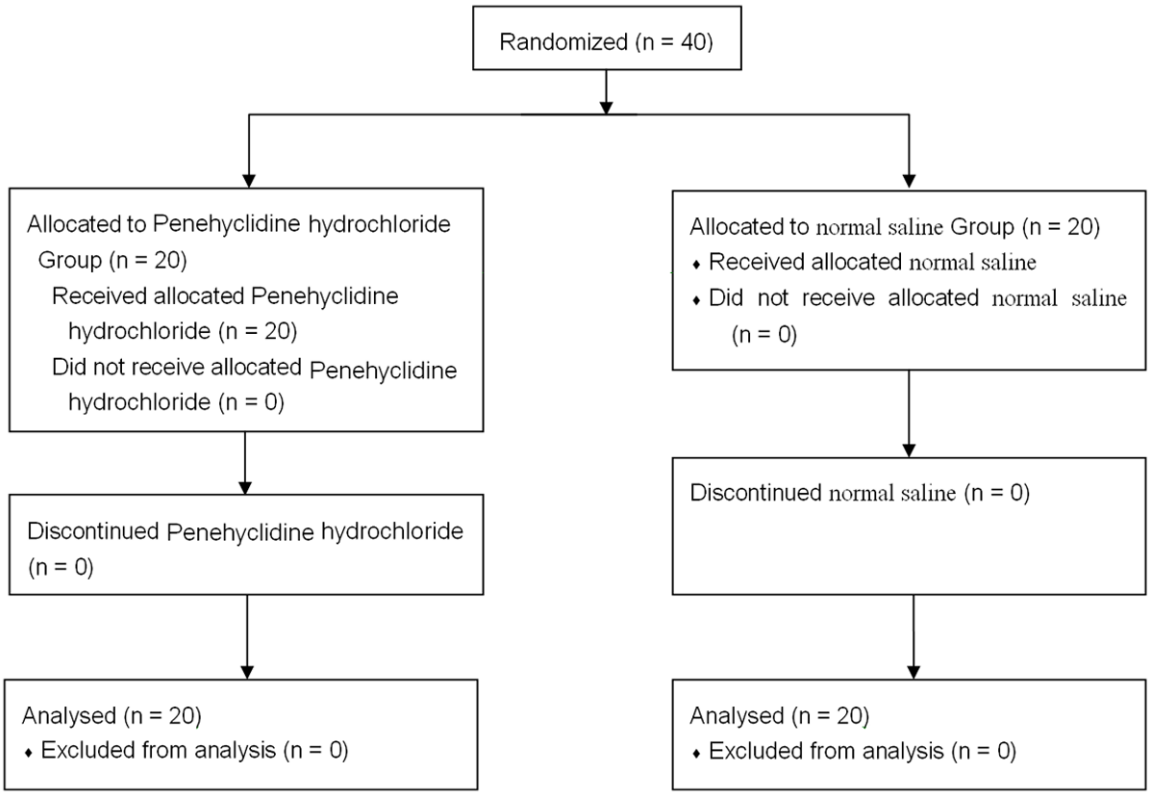


**Figure 1.** Consort diagram showing the flow of participants through each stage of a randomized trial.

The study protocol was approved by the Institutional Review Board of West China Hospital, Sichuan University and registered in Chinese Clinical Trial Registry (ChiCTR-TRC-14004692, http://www.chictr.org/cn/). Informed written consents for the study were obtained from all patients. Forty patients, ASA physical status I or II, aged 18 - 65 yr, undergoing elective laparoscopic cholecystectomy with general anesthesia, were recruited. Exclusion criteria included obesity (Body Mass Index > 28 kg/m$^2$), pregnancy, risk of aspiration of gastric contents, suspected or known difficult airway, and contraindication to propofol, with cardiovascular and neurological diseases, impairment of renal, hepatic function, hearing impairment, substance abuse and those taking drugs affecting the consciousness. No sedative or opioid drugs were administered before induction of anesthesia. According to the computer-generated list and sealed opaque envelope technique, patients were randomly assigned to 1 of 2 groups: PH (Group PH) or normal saline (Group NS), 20 in each group (**Figure 1**).

After arrival in preparation room for anesthesia, a 20 G venous cannula was inserted into forearm vein by nurse and then lactated Ringer's solution (5 ml/kg) was administered. Before drug administration, standard monitoring included electrocardiography (ECG), pulse oximetry and non-invasive arterial pressure were established. Processed EEG parameters were acquired with a BIS monitor (Aspect Medical Systems, Newton, MA, USA). Sensors were positioned according to the manufacturer instructions. When each patient was comfortable on the operating table for 5 min, PH 0.012 mg/kg (diluted to 10 ml, up to 1 mg) or normal saline (same volume) prepared by the research nurse was administered 30 min before induction of anesthesia. During induction, the patients breathed 100% oxygen through a face mask. Propofol was administered via a Graseby 3500 syringe pump (SIMS Graseby Ltd., Herts, England) using the infusion program RUGLOOP [5]. Effect compartment controlled administration was used. A three-compartment model with an enlarged effect-site compartment was used [6]. The effect-site equilibration constant, $k_{e0}$, was computed to yield a time to peak effect of 1.6 min after bolus injection, yielding a $t_{1/2}$ $k_{e0}$ of 34 s [7]. The target effect-site concentra-

**Table 1.** Patients' characteristics

| | Group PH | Group NS |
|---|---|---|
| Sex (M/F) | 7/13 | 8/11 |
| Age (years) | 45 ± 7 | 41 ± 8 |
| Weight (kg) | 57.3 ± 8.9 | 60.5 ± 9.0 |
| Height (cm) | 163 ± 6 | 163 ± 7 |
| BMI (kg/m$^2$) | 21 ± 3 | 23 ± 3 |
| Baseline Values | | |
| BIS | 97.4 ± 0.7 | 97.5 ± 0.7 |
| MAP | 83.0 ± 9.1 | 85.1 ± 7.2 |
| HR | 79.5 ± 12.1 | 77.6 ± 12.4 |
| RPP | 9323 ± 1925 | 9352 ± 1895 |

Values are means ± SD or number. BMI = Body Mass Index; MAP = mean arterial pressure; HR = heart rate; RPP = rate-pressure product.

tion of propofol was first set at 1.0 μg/ml and it was increased by 1.0 μg/ml every 4 min (up to 4.0 μg/ml) until the clinical endpoint was achieved (loss of consciousness). Then, ventilation was assisted manually and the trachea was intubated after the intravenous administration of fentanyl 2.0 μg/kg and rocuronium 0.6 mg/kg.

Baseline measurements of BIS, mean arterial pressure (MAP), heart rate (HR) and pulsed oxygen saturation ($SpO_2$) were taken by another anesthesiologist. During induction, BIS values, MAP, HR and $SpO_2$ were recorded every minute and the Observer's Assessment of Alertness/Sedation (OAA/S) rating scale was recorded every 30 seconds (score 5 = awake and responds readily to name spoken in normal tone; 4 = lethargic response to name in normal tone; 3 = response only after name is called loudly and/or repeatedly; 2 = response only after name is called loudly and after mild shaking; 1 = does not respond when name is called and after mild shaking). OAA/S rating scale was assessed by an independent observer who was blinded to the drugs given. In order to decrease the influence of OAA/S rating scale to other monitoring measurements, we record results by turns of BIS, MAP, HR, and OAA/S. We also calculated the rate-pressure product (RPP) based on MAP and HR at every time point. Onset of anesthesia was confirmed with disappearance of the eyelash reflex. The induction time was taken as time from the start of propofol infusion to loss of consciousness and the induction dose as the amount of propofol administered in that time. Predicted effect-site propofol concentration (Ce) and the total propofol dose were recorded from the TCI pump when the loss of consciousness was achieved. During the procedure, we must guarantee patients to be stable, and all patients were administered oxygen without limitation, supplied ventilatory support if necessary. If severe incidents appeared, or any extra-intervention given, the research was discontinued and the patient would be excluded.

Statistical analysis was conducted using SPSS for Windows 13.0 (SPSS Inc., Chicago, Illinois). Our sample size calculation was based on previously published variances in propofol steady state requirements and a predicted treatment effect of 25%, using mean ± SD values of 4.0 ± 1.0 and 3.0 ± 1.0, a type I error 0.05 and a type II error of 0.80. The sample size estimation was 34 subjects with complete data. A quantal response model (probit analysis) was used to calculate $Ce_{05}$, $Ce_{50}$ and $Ce_{95}$ at the end-point based on predicted effect-site propofol concentrations. Numerical data are expressed as mean ± SD. Statistical analyses were performed using Student's t test or ANOVA. A $P$ value < 0.05 was considered statistically significant.

## Results

Patients' demographics and baseline measurements of MAP, HR and BIS were comparable between two groups (**Table 1**). Induction of anesthesia was smooth in all cases. Hemodynamic variables remained stable and no significant hypotension occurred. There were no significant differences for MAP, HR and BIS at each time point between two groups (**Table 2**).

The time to reach end point (loss of consciousness) was shorter in Group PH than Group NS [(618 ± 72) s vs. (683 ± 88) s, P = 0.016]. The propofol Ce and consumption based on body weight of each patient were lower in Group PH than Group NS [(1.83 ± 0.24) mg kg$^{-1}$ vs. (2.05 ± 0.32) mg/kg, P = 0.016 and (2.19 ± 0.29) μg/ml vs. (2.42 ± 0.30) μg/ml, P = 0.021, respectively]. BIS values were not significantly changed before propofol infusion in both groups and decreased gradually as propofol Ce increased, and were not significantly different when end point was reached between two groups [71.1 ±

**Table 2.** Patients' parametric changes during induction of anesthesia

| | Group | OAA/S | | | | |
|---|---|---|---|---|---|---|
| | | 5 | 4 | 3 | 2 | 1 |
| Time (s) | PH | 0 | 274.3 ± 68.7 | 387.5 ± 78.6* | 514.4 ± 97.6 | 618.4 ± 72.0* |
| | NS | 0 | 303.3 ± 73.3 | 483.9 ± 78.5 | 566.2 ± 90.0 | 683.1 ± 87.9 |
| Dose of propofol (mg/kg) | PH | 0 | 0.66 ± 0.21 | 1.04 ± 0.25* | 1.46 ± 0.34 | 1.83 ± 0.24* |
| | NS | 0 | 0.77 ± 0.20 | 1.29 ± 0.26 | 1.66 ± 0.3 | 2.05 ± 0.31 |
| Ce of propofol (μg/ml) | PH | 0 | 0.81 ± 0.24 | 1.31 ± 0.27* | 1.77 ± 0.35* | 2.18 ± 0.29* |
| | NS | 0 | 0.97 ± 0.26 | 1.61 ± 0.27 | 2.00 ± 0.32 | 2.42 ± 0.30 |
| BIS | PH | 97.3 ± 1.1 | 92.5 ± 5.7 | 81.5 ± 5.5 | 77.5 ± 3.4 | 71.1 ± 10.8 |
| | NS | 97.7 ± 0.6 | 90.6 ± 6.3 | 80.0 ± 6.1 | 73.8 ± 6.4 | 67.4 ± 7.2 |
| MAP (mmHg) | PH | 82.6 ± 9.7 | 79.7 ± 8.5 | 75.2 ± 7.6 | 74.3 ± 7.9 | 73.9 ± 9.5 |
| | NS | 84.3 ± 7.9 | 76.3 ± 7.5 | 73.4 ± 7.0 | 71.3 ± 6.3 | 70.4 ± 7.2 |
| HR (bpm) | PH | 76.7 ± 13.2 | 74.7 ± 11.7 | 74.7 ± 10.6 | 73.1 ± 11.1 | 73.6 ± 12.1 |
| | NS | 76.2 ± 13.2 | 72.1 ± 11.5 | 71.5 ± 9.5 | 72.9 ± 10.1 | 72.4 ± 10.4 |
| RPP | PH | 9283 ± 2220 | 8443 ± 1828 | 8043 ± 1482 | 7431 ± 2228 | 7525 ± 1567 |
| | NS | 9384 ± 1888 | 7964 ± 1342 | 7569 ± 1159 | 7626 ± 1269 | 7388 ± 1350 |

Values are mean ± SD. *$p < 0.05$ compared with Group NS. OAA/S = Observer's Assessment of Alertness/Sedation rating scale; Ce = effect-site concentration; BIS = Bispectral Index; MAP = mean arterial pressure; HR =heart rate; RPP = rate-pressure product.

**Table 3.** Predicted $Ce_{05}$, $Ce_{50}$ and $Ce_{95}$ values of propofol for loss of conscious with 95% Confidence Intervals

| | Group PH | Group NS |
|---|---|---|
| $Ce_{05}$ | 1.61 (1.41, 1.74) | 1.80 (1.64, 1.90) |
| $Ce_{50}$ | 2.12 (2.05, 2.15) | 2.28 (2.21, 2.34) |
| $Ce_{95}$ | 2.63 (2.53, 2.78) | 2.76 (2.66, 2.90) |

10.8 vs 67.4 ± 7.2, $P > 0.05$). The predicted $Ce_{05,}$ $Ce_{50}$ and $Ce_{95}$ values of propofol for loss of conscious were showed in **Table 3**.

All recruited patients were hemodynamically stable throughout anesthesia induction and none of the patients required assisted or mechanical ventilation. During the early postoperative period, no neurological adverse events were reported.

## Discussion

The present study indicates that premedicated PH decreased the dose of propofol required for anesthetic induction, i.e. to reach the predefined pharmacodynamic end-point, loss of consciousness. To the best of our knowledge, this is the first study to describe that the pharmacodynamics of propofol during the induction of anesthesia was altered by the administration of PH.

The induction dose of propofol was influenced by many factors. It has been reported that age, lean body mass and degree of anxiety affected the anesthetic requirement of propofol [8-10]. In addition to these factors, several studies suggested that cardiac output (CO) is the determinant of propofol induction of anesthesia dose [11-14]. Takizawa et al. reported that the propofol requirements for the induction of anesthesia were increased and propofol concentrations were decreased during continuous infusion by the administration of an anticholinerigic drug - atropine [15]. In our study, the study drug we used is a new anticholinerigic drug. However, we found that the decreases of doses and concentration of propofol following the administration of PH could not be related to CO because PH was associated with few cardiovascular effects. This phenomenon can be explained by no significant changes of MAP, HR and RPP during the period of study although we did not determine CO in our study. As there were no statistically significant differences in cardiovascular data between groups, it is not likely that hemodynamics influenced propofol requirements.

To assess the anesthetic requirements in relation to the depth of sedation/anesthesia, we

used a combination of the TCI, the OAA/S, and the BIS monitor. We investigated the effect of premedicated PH on BIS both as a sole anesthetic and as an adjunct to general i.v. anesthesia. The BIS monitor is a proprietary algorithm that translates electroencephalographic data into a numerical value, 100 (awake) to 0 (isoelectric EEG). Several studies have reported that BIS is a reliable predictor of the level of sedation and loss of consciousness [15, 16]. Interestingly, we found that there were no significant changes of BIS values before and after administration of PH in both groups, which means PH has no impact on BIS value. And our results showed that the changes of BIS values were similar as TCI propofol was started in both groups. However, PH reduced significantly both dose and Ce of propofol from $OAA/S_3$ until loss of consciousness and shortened the time to reach end point (loss of consciousness), which indirectly means PH has sedative effect to some degree. The causes that PH has sedative effect and reduces both dose and Ce of propofol for loss of consciousness but does not alter BIS values are not clear. The algorithm that computes the BIS evaluates predominantly three features of the EEG: the ratio of very high β-range activity to high α plus low β activity (relative β ratio), very high β-range phase relationships and burst suppression phenomena. These features are used sequentially by the algorithm as sedation and anesthesia increases, with relative β ratio being the most influential feature during light sedation. We hypothesize that PH may activate certain spectral regions of EEG not detected by the BIS algorithm. Similarly, Meuret et al. showed that the auditory steady state response and BIS are not reduced after administration of 8.6 μg/kg intravenous anticholinergic drug scopolamine in propofol-anesthetized subjects [17].

The mechanism of central sedative action of PH is still not completely understood. At least part of the effect is believed to be mediated via the central cholinergic system. Cholinergic neurotransmission is also a potential mediator of general anesthetic actions by propofol [18]. Because of neural activity of muscarinic receptors, at clinical dose, PH exerts as same an effect as scopolamine on the central nervous system (CNS). So propofol could mediate its effect on consciousness by interfering with nicotinic transmission, and the administration of PH, via inhibition of central muscarinic transmission, simply augments the depth of anesthesia. In a previous study, Meuret et al. suggested that the scopolamine be administered before propofol [17], then as a result of the additive CNS depressant effects, it is possible that a lower dose of propofol would have been necessary to produce unconsciousness. The amnesic effect of PH, just like scopolamine, results principally from a blockade of postsynaptic cholinergic muscarinic $M_1$ transmission [19].

A few limitations in our study should be kept in mind. First, the presented concentration is a predicted value that is calculated from a pharmacokinetic model, and not real measurement from patients' plasma sampling. This predicted effect site concentration is estimated from Marsh's pharmacokinetic model, however it is known that propofol can be administered by this method with acceptable bias and inaccuracy in clinical situations [5]. Second, we tested PH in people younger than 55 yr, and we do not know whether it can produce significant psychomotor effect in older patients (age > 65 yr).

In summary, there was an additive interaction between PH and propofol for loss of consciousness. Propofol requirement for the induction of anesthesia was decreased by the administration of PH. PH has sedative effect but has no impact on BIS.

## Disclosure of conflict of interest

None.

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