Review Article

Application of different infusion methods of propofol in intravenous anesthesia: a narrative review

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Objective: To collect and summarize the advantages and disadvantages of propofol infusion modes currently used in clinical practice, and provide ideas for improving the controllability and accuracy of propofol administration in intravenous anesthesia.

Background: Propofol is widely used to induce sedation in various minimally invasive procedures such as hysteroscopy gastrointestinal endoscopy and cystoscopy. It is a short-acting anesthetic which has been used clinically for intravenous anesthesia for over 30 decades benefit from its fast onset, rapid systemic clearance and low incidence of nausea and vomiting. There are three infusion methods of propofol, including vital signs guided conventional infusion, plasma- or effect-site targeting guided open-loop controlled infusion and EEG devices targeting guided closed-loop controlled infusion. The conventional mode of propofol infusion is experimental which mainly based on vital signs, using continuous infusion by infusion pump or intermittently manual infusion. The target controlled infusion mode is constantly calculated by the computer based on the multicompartment and pharmacokinetic model for achieving and maintaining the predetermined plasma or effector site target concentration. The use of propofol in intravenous anesthesia has significantly improved the quality of procedures. However, the accuracy and overall controllability of propofol administration are still poor, resulting in ventilatory impairment, delayed resuscitation, intraoperative awareness, and body movement which may affect safety and patient satisfaction. Hence, how to choose an appropriate mode of propofol infusion, maintain more stable depth of anesthesia according to the patient's condition and operation stimulation has always been the concern of anesthesiologists. The present review aimed to summarize the current infusion methods of propofol in intravenous anesthesia.

Methods: Literature related to propofol was searched in PubMed database, including the advantages, side effects and infusion modes of propofol, especially the cutting-edge application mode of propofol.

Conclusions: Propofol is commonly used sedative in intravenous anesthesia. This review summarized three current infusion methods of propofol, each of which has its advantages and disadvantages. Challenges of imprecise pharmacokinetic parameter estimates and effect measures still remain. Further studies which focus on pharmacokinetics models and real-time monitoring propofol blood concentrations technology, are needed to achieve precision medication and better overall control of anesthesia.

Keywords: Propofol; infusion; intravenous anesthesia

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Introduction

Propofol, 2,6-diisopropyl phenol, alkyl phenol derivative, is a short-acting intravenous hypnotic drug that is used for induction and maintenance of sedation and general anesthesia. It exerts its effects through potentiation of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) at the GABAA receptor (1). Propofol is usually co-administered with opioid analgesics as intravenous anesthesia for hysteroscopic examination or therapeutic surgery (2). There are three current infusion methods of propofol, including vital signs guided conventional infusion, plasma- or effect-site targeting guided open-loop controlled infusion and EEG devices targeting guided closed-loop controlled infusion. The short-acting anesthetic has been used clinically for intravenous anesthesia for over 30 decades benefit from its fast onset, rapid systemic clearance and low incidence of nausea and vomiting (3,4).

However, the challenges remain in the clinical implications of propofol. Firstly, pain on injection is the most common adverse effect of propofol. On average, 70% of patients reported pain on injection with a higher incidence in pediatric patients (5,6). Secondly, there is still some debate about its safety and accuracy of propofol TCI. Obvious limitations were reported in vital signs guided conventional infusion, such as underdose/overdose, ventilatory impairment, delayed resuscitation, intraoperative awareness, and body movement (7). Despite myriad pharmacokinetic-pharmacodynamic studies about propofol TCI, there is still no optimal model (6). The imprecise pharmacokinetic parameter estimates and effect measures are associated with variability. Hence, the anesthesiologist should both use smart infusion pumps as the basis and use experience to titrate the intravenous agents, to avoid the adverse effects. At present, there is no relevant review for guiding choose an appropriate mode of propofol infusion. The aim of the present article is to review the current infusion methods of propofol in intravenous anesthesia.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/dmr-21-49).

Modes of propofol infusion

Vital signs guided conventional infusion

Currently, the conventional mode of propofol infusion is experimental which mainly based on vital signs, using continuous infusion by infusion pump or intermittently manual infusion. Vital signs used to determine the depth of anesthesia include blood pressure, heart rate, eye movement, respiratory rhythm, swallowing activity, skin temperature, body movement, etc. (8). Vital signs comprehensively reflect stress caused by surgical stimulation and the inhibitory effect of anesthetics. However, due to the low specificity, great individual variation and lack of relevant pharmacodynamics and pharmacokinetics evidence, propofol infusion based on vital signs may not be able to provide stable sedation quality for patients (9,10). Intermittently manual infusion not only increases anesthesiologists' workload, but also causes blood concentration of propofol peaks and dips repeatedly. When there is a strong stimulation such as endoscope intubation, patients might be restless and higher dosage of propofol is required which may lead to hypoxemia, apnea and hypotension (11). Claeys *et al.* (12) found that continuous infusion of propofol could stabilize blood drug concentration at an appropriate level, which had better cardiovascular stability than single administration. Roberts *et al.* (13) proposed the famous 10-8-6 regimen, which could maintain the relative stability of blood drug concentration. Conventional mode of propofol infusion may be convenient, but there is some obvious limitation such as underdose/overdose, ventilatory impairment, delayed resuscitation, intraoperative awareness, and body movement which may affect safety and patient satisfaction (7).

Open-loop target controlled infusion (TCI)

TCI is a computer-controlled drug infusion technique which is designed to achieve a predetermined plasma or effector site target concentration. The infusion rate is constantly calculated by the computer based on the multicompartment pharmacokinetic model for achieving and maintaining the target concentration (14). The pharmacokinetic model most commonly used in TCI systems is the open 3-compartment model. Classical infusion models include "Marsh", "Schnider", "Eleveld", and "Kataria" models. TCI has been developed as a conventional infusion system for propofol administration based on the pharmacokinetics and pharmacodynamics (15,16). TCI of propofol was associated with faster induction, faster recovery time, better hemodynamic and respiratory stability than manual infusions (17-19). There are two kinds of TCI infusion system: open-loop control and closed-loop control. The open-loop controlled infusion system is programmed with pharmacokinetic model based on either plasma- or effect-site targeting. With effect-site targeting, the plasma propofol concentration would be briefly increased to an optimal level above the target effect-site concentration, resulting in significant hemodynamic instability. In contrast, plasma-site targeting TCI system is relatively stable. Finally, the disadvantages of the two currently open-loop controlled TCI system are that the significantly differ of induction doses and individual variability (20,21).

Bispectral Index Scale (BIS)-guided closed-loop target-controlled infusion

Closed-Loop target-controlled infusion systems consist of a 'brain'—a central operating system with built-in algorithms—an 'effect'—a target control variable—and an 'actuator'—a drug delivery system, such as a syringe pump. These three elements are connected by a feedback system, which allows the automated control of drug delivery in order to maintain a pre-set target value of the control variable without any manual input. Greater stability personalized precision anesthesia may be achievable. The performance of a closed-loop system for anesthesia depends on the reliability of the control variable. BIS-guided closed-loop delivery of anesthetics has been extensively studied recently. It was reported that BIS had a good correlation with the plasma concentration of propofol (22). Ludbrook *et al.* (23) found that there was a close relation between brain concentrations and bispectral index, although with considerable interpatient variability. It's widely reported when compared with manual control, BIS-guided anesthetic delivery of total IV anesthesia reduces propofol requirements, better maintains a target depth of anesthesia, reduces recovery time and better control blood pressure (24-26). However, the imprecise pharmacokinetic parameter estimates and effect measures due to individual variability still remain.

Narcotrend guided target-controlled infusion

Narcotrend, an EEG index designed to measure the depth of anesthesia, has been confirmed to be effective as a continuous measure of the depth of sedation (27). Narcotrend is based on analyzing the EEG signal, and it classifies the degree of hypnosis by grades A to F (28). Kreuer *et al.* (29) indicates that Narcotrend is effective to facilitate a significant reduction of recovery times and propofol consumption when used for guidance of propofol titration during a propofol-remifentanil anesthetic. Rundshagen *et al.* (30) points out that guidance of anaesthesia with the Narcotrend-monitor leads to fewer deviations from a defined target than clinical assessment of anaesthetic depth only and lower scores of nausea in the immediate period after anaesthesia. Researches show that there is a good correlation between Narcotrend index and BIS: the Narcotrend stages D or E are assumed equivalent to BIS values between 64 and 40 indicating general anaesthesia (30). Studies have reported that Narcotrend Index had a close correlation with the calculated propofol effect compartment concentrations (31,32). However, most of researches on Narcotrend guided target-controlled infusion are focused on open-loop models, whether Narcotrend index can be used as a control variable for closed-Loop target-controlled infusion systems remained inconclusive and required further study.

Entropy guided target-controlled infusion

The Entropy assesses the randomness of the EEG via a previously published algorithm and generates two indices: state entropy (SE) and response entropy (RE) (33). Although SE is computed from a frequency range (0.8–32 Hz) that is dominated by the EEG activity, RE's broader frequency range (0.8–47 Hz) includes higher frequencies that are still part of the electromyogram domain. Entropy analysis can be performed in time or frequency domains (spectral entropy), and can also detect nonlinear signal correlations (34). It has been reported that the entropy index has a good correlation with propofol (35), and its reaction is quick and sensitive. RE (Reaction Entropy) increases significantly about 4 min before the increase of BIS. In addition, the entropy index is better than BIS in resisting interference such as electrotome (36). Spectral entropy is a safe and reliable method for anesthesia depth monitoring. Vakkuri *et al.* (37) reported that entropy monitoring assisted titration of propofol, by keeping the state entropy value between 45 and 65, decreased consumption of propofol, and shorter recovery times in the entropy group. However, frequent eye movements, coughing, and body movements can create false entropy and interfere with the measurement of entropy. Patients' physiological conditions, such as age (38) and hypothermia (39), can also affect EEG signal. The accuracy of its application in the guidance of target-controlled infusion of propofol needs to be improved.

Auditory evoked potentials index (AAI) guided target-controlled infusion

Auditory evoked potentials (AEP) have been reported to fulfils many of the requirements for measurement of the level of anesthesia. By using the AAI as the input signal for the closed-loop control system in patients undergoing surgery while breathing spontaneously, Kenny and colleague (40) believed that they had validated this measurement technique as an assessment of the level of anesthesia during maintenance with propofol. Kreuer *et al.* reported wide variation in the awake values and considerable overlap of AAI values between consciousness and unconsciousness during propofol-remifentanil anesthesia, suggests further improvement of the AAI system is required (41).

Conclusions

Propofol is the most commonly used sedative in intravenous anesthesia, different applications of have been widely studied. This review summarized three current infusion methods of propofol, each of which has its advantages and disadvantages. Challenges of imprecise pharmacokinetic parameter estimates and effect measures remain yet. Further studies which focus on pharmacokinetics models and real-time monitoring propofol blood concentrations technology, are needed to achieve precision medication and better overall control of anesthesia.

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Footnote

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