Propofol Infusion for Induction and Maintenance of Anesthesia in Elderly Patients: Recovery and Hemodynamic Profiles

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Study Objective: To evaluate the effect of propofol infusion for both induction and maintenance of anesthesia on hemodynamics and recovery in elderly patients compared with conventional thiopental isoflurane anesthesia.

Design: Randomized, prospective, study.

Setting: Teaching hospital.

Patients: 60 nonpremedicated ASA physical status I, II, and III adult elderly patients scheduled to undergo total hip replacement surgery.

Interventions: Patients received either intravenous propofol infusion at 0.75 mg/kg/min or thiopental bolus 2 to 4 mg/kg for induction, followed by variable-rate propofol infusion up to 0.15 mg/kg/min or isoflurane 0.5% to 1.5% for maintenance of anesthesia. Nitrous oxide and fentanyl supplements were given in all patients.

Measurements and Main Results: Perioperative hemodynamic changes, patient recovery profile, and myocardial ischemia incidents were assessed in both anesthetic groups. Induction of anesthesia by propofol infusion (1.6 mg/kg) did not produce significant hypotension (-8.3% ± 5.5%) or bradycardia; these changes were similar to induction by thiopental bolus injection (3.3 mg/kg). Furthermore, increases in blood pressure and heart rate (HR) during endotracheal intubation were limited to 6% following propofol induction compared with 22% for thiopental induction. During maintenance of anesthesia, the decrease in MAP and HR was comparable in both anesthetic groups. Postanesthetic recovery times for patient to achieve wakefulness, mental orientation, and a maximum Aldrete score (10) were significantly faster in the propofol group, by 4 minutes, 6 minutes, and 20 minutes, respectively; however, the time to discharge from the postanesthesia care unit was not different. Holter-monitored perioperative myocardial ischemic events detected in 23% of the patients occurred independent of hemodynamic changes or the type of anesthetic administered.

Conclusion: Induction of anesthesia by propofol infusion in elderly patients produces greater attenuation of cardiovascular sympathetic response than thiopental bolus induction. Induction and maintenance of anesthesia by propofol infusion results in more rapid recovery in our elderly patients than thiopental isoflurane anesthesia.

Keywords: Anesthetic techniques: general; anesthetics, intravenous: propofol, thiopental sodium; anesthetics, volatile: isoflurane; complications: myocardial ischemia; recovery: assessment.
Original Contributions

Introduction

Induction of anesthesia by bolus administration of propofol can produce significant hypotension, i.e., a 15% to 40% decline in systolic blood pressure (SBP). Because of its negative inotropic and vasodilatory effects, propofol produces a greater degree of cardiovascular depression than does an equipotent dose of thiopental. The degree of hypotension is influenced by both the rate of propofol administration and the total dose, and this is exaggerated, especially in elderly patients. Despite downward adjustment of the propofol induction dose in the elderly population, hypotension occurs more often than with thiopental. Consequently, propofol may predispose to a higher risk of myocardial ischemia in elderly patients with preexisting coronary artery disease (CAD).

On the other hand, propofol has distinct pharmacokinetic advantages that include rapid drug elimination and a lack of cumulative effects. Mental alertness and "home-readiness" following administration of a single bolus and a short-duration maintenance infusion are more rapid than that with thiopental induction and inhalational anesthesia in young patients. However, evidence of superior propofol recovery is less convincing for procedures of longer duration (greater than 120 minutes) and has not been demonstrated in elderly patients.

Accordingly, we sought to determine whether slowing the rate of induction of anesthesia by administering propofol by slow, continuous infusion would minimize hemodynamic derangement and the risk of myocardial ischemia in elderly patients. Furthermore, we sought to determine whether maintenance of anesthesia by propofol infusion provides more rapid emergence and recovery than thiopental-isoflurane anesthesia for surgery lasting approximately 120 minutes.

Materials and Methods

With approval from the Toronto Hospital Ethics Committee and patient informed consent, we prospectively studied 60 ASA physical status I, II, and III patients aged 65 to 85 years, scheduled to undergo total hip replacement surgery. Patients with significant cardiovascular, respiratory, hepatic, or renal disease were excluded from study. On the evening prior to surgery, triazolam 0.125 to 0.25 mg was administered as a hypnotic to patients when requested. Routine antihypertensive and antianginal medications were continued until the morning of surgery.

Anesthetic Protocol

Patients were randomized by a computer-generated list to either a propofol infusion induction-maintenance regimen or thiopental induction-inhalation (isoflurane) anesthesia maintenance. Preoperative medication was not administered. Prior to induction, all patients were prehydrated with 10 ml/kg of intravenous crystalloid solution (Plasmalyte), then given vecuronium 1 mg and fentanyl 0.75 μg/kg. In the propofol group, anesthesia was induced by propofol infusion at 0.75 mg/kg/min via an electronic pump (IVAC). In the thiopental group, induction was achieved by bolus injection of 2 mg/kg, titrated to a total of 4 mg/kg within 60 seconds as necessary. Following induction, succinylcholine 1.0 to 1.5 mg/kg was given to facilitate endotracheal intubation. Timing of intubation was indicated by the loss of muscle twiching tested with a peripheral nerve stimulator. Glycopyrrolate was not given prophylactically.

In patients given propofol, anesthesia was maintained with a variable-rate propofol infusion up to 0.15 mg/kg/min, and 60% nitrous oxide (N₂O) in oxygen (O₂). In the thiopental-isoflurane group, anesthesia was maintained at 0.5% to 1.5% isoflurane end-tidal concentration and 60% N₂O in O₂. In both groups, maintenance doses were adjusted to provide optimal anesthetic and surgical conditions while maintaining hemodynamic stability. When the patient's blood pressure (BP) and/or heart rate (HR) increased by 25% from baseline, maintenance propofol infusion or isoflurane inhalation was increased by 50% and in the thiopental-isoflurane group, anesthesia was maintained at 0.5% to 1.5% isoflurane end-tidal concentration and 60% N₂O in O₂. In both groups, maintenance doses were adjusted to provide optimal anesthetic and surgical conditions while maintaining hemodynamic stability. When the patient's blood pressure (BP) and/or heart rate (HR) increased by 25% from baseline, maintenance propofol infusion or isoflurane inhalation was increased by 50% and tentany 1 μg/kg was administered (total intraoperative fentanyl dose was limited to a maximum of 4 μg/kg). The anesthetic dose was reduced by the same magnitude when a similar reduction of hemodynamic parameters was observed. Intraoperative muscle relaxation was provided as needed by administration of incremental doses of vecuronium 0.04 to 0.06 mg/kg, aiming to maintain 2/4 on the train-of-four assessment. Ventilation was controlled to maintain arterial oxygen saturation above 98% and CO₂ at 35 mmHg as measured by end-tidal monitoring.

Approximately 5 minutes before the end of surgery, propofol infusion or isoflurane inhalation was discontinued; N₂O and O₂ were continued until the end of surgery. Neuromuscular blockade was reversed with IV neostigmine 2.0 mg and glycopyrrolate 0.4 mg. In the postanesthesia care unit (PACU), patient analgesia was managed by IV administration of incremental doses (2 to 4 mg) of morphine as needed.

Measurements

The time to induction of anesthesia was recorded as the time from the start of drug administration to the loss of eyelash reflex. The time to intubation also was recorded. Duration of anesthesia was reported as the time from the start of drug administration to the time of patient extubation.

Intraoperative hemodynamic measurements—HR, SBP, diastolic blood pressure (DBP), and mean arterial pressure (MAP) were obtained noninvasively using ECG (3-lead ECG) and oscillometry (Dinamap, Critikon, Tampa, FL) at the following intervals: 1 minute before induction (baseline), every minute for 10 minutes after induction, and every 5 minutes thereafter throughout surgery. Hypotension was defined as SBP of 90 mmHg or less or a decline of at least 30% from baseline, and was treated by reduction of anesthetic dose followed by IV ephedrine in 5 mg increments. Bradycardia was defined as HR less than 50 beats per minute (bpm) and was treated with IV glycopyrrolate 0.4 mg.
Myocardial ischemia was assessed perioperatively using continuous Holter ECG (5-lead) (model 8500, Applied Cardiac Systems) monitoring beginning 1 hour before surgery until 24 hours postoperatively. Holter ECG evidence of myocardial ischemia was defined as ST-segment change of 1.0 mm or greater from baseline. Both the frequency and duration of ST-segment changes were documented. Holter ECG data were analyzed by investigators who were blinded to the patient’s anesthetic regimen. A follow-up 12-lead ECG and a cardiac enzyme (CPK-MB) measurement were obtained at 24 hours postoperatively.

Postoperative patient recovery in the PACU was assessed by an independent investigator who was blinded to the intraoperative anesthetic regimen. The times to extubation, wakefulness, and mental alertness after discontinuation of N2O were evaluated by the patient’s responsiveness to verbal commands and orientation to name, time, and place. Each patient also was evaluated using the Aldrete recovery scoring system, which evaluates five criteria on a scale of 0 to 9, permitting a possible maximum score of 10. Criteria include (1) activity, where 2 = movement of four extremities voluntarily or on command, 1 = movement of two extremities, and 0 = no movement; (2) respiration, where 2 = deep breathing and coughing, 1 = limited breathing, 0 = apnea; (3) circulation, where 2 = BP ≥ 20% of preanesthetic level, 1 = BP ≥ 20% to 50% of baseline, and 0 = BP < 50% of baseline; (4) consciousness, where 2 = fully awake, 1 = arousable, 0 = unresponsive; and (5) color, where 2 = normal color, 1 = pale or dusky, 0 = cyanotic. Aldrete scores were recorded every 15 minutes until two consecutive scores of 10 were obtained prior to discharge from the PACU. PACU discharge time was recorded as the time from discontinuation of N2O to PACU discharge. The occurrence of postanesthetic nausea, emesis, and any other complication related to surgery or anesthesia was recorded until hospital discharge.

Data are reported as means ± SD and were analyzed using t-test, analysis of variance ANOVA, or Chi-square analysis where appropriate. A p-value less than 0.05 was considered statistically significant.

Results

Of the 60 patients undergoing total hip replacement surgery, 29 were randomized to the propofol group and 31 to the thiopental-isoflurane group. Fifteen patients in each group were greater than 70 years old, but no significant differences in age, gender, weight, or ASA status were found between the two anesthetic groups (Table 1). The total intraoperative administered doses of succinylcholine, fentanyl, and vecuronium also were similar (Table 2).

Dose Requirement and Duration of Anesthesia

The dose of propofol required for induction of anesthesia by infusion was significantly lower than the dose of thiopental required for bolus induction [113.1 ± 42 mg (±1.6 mg/kg) vs. 229.6 ± 65 mg (±3.3 mg/kg)]. Propofol main-

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<th>Table 1. Patient Characteristics, Duration of Anesthesia, Blood Loss and Fluid Replacement</th>
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<td>Duration of anesthesia (min)</td>
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Note: Values are expressed as means ± SD. STP = thiopental sodium.

Hemodynamics

Hemodynamic changes immediately following induction of anesthesia were negligible in both study groups. Specifically, propofol induction by infusion did not produce significant hypotension: the mean maximum decline in SBP was only 8.3 ± 5.5%, compared favorably to 6.3 ± 3.4% following thiopental induction.

However, the hemodynamic response to laryngoscopy and intubation differed significantly in the two study groups. Parameters remained stable in the propofol group, which manifest mean changes of -3.5 ± 6.5% in SBP, 5.8 ± 5.9% in DBP, 4.5 ± 5.6% in MAP, and 5.5 ± 3.8 HR. In contrast, mean maximum increases in the thiopental-isoflurane group were SBP: 17.2 ± 3.8%, DBP: 29.3 ± 5.1%, MAP: 22.2 ± 5.0%, and HR: 22.2 ± 4.2% (p < 0.05) (Figures 1–3). Within 5 to 6 minutes after the start of in-

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<th>Table 2. Dosage of Intraoperative Anesthetic Medications and Time to Complete Induction and Intubation</th>
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<td>Induction dose (mg)</td>
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<td>Succinylcholine (mg)</td>
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<td>Fentanyl (µg)</td>
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Note: Values are expressed as means ± SD. STP = thiopental sodium. *p < 0.05 between propofol and thiopental-isoflurane groups.

duction, these values had returned to baseline in both groups.

From 8 to 9 minutes postinduction until the end of anesthesia, all hemodynamic variables remained significantly lower than baseline in both study groups (Figures 1–3). Intraoperative hypotension (SBP ≤ 90 mmHg) was recorded in 13 patients (8 in the propofol group and 5 in the isoflurane group), all of whom were treated successfully with IV ephedrine. The dose of ephedrine was 10 ± 7.9 mg (mean ± SD). Glycopyrrolate was not required to treat bradycardia in any patient. Postoperatively, hypertension was detected in 38 patients (63.3%) in the PACU, 19 patients in each anesthetic group.

Myocardial Ischemia

Myocardial ischemia was detected perioperatively by Holter ECG in 14 patients (5 in the propofol group and 9 in the thiopental-isoflurane group). Of these 14 patients, 12 were over 70 years of age; one of the 14 had known atherosclerotic heart disease, and 5 of the 14 had preexisting hypertension.

Over a total of 16 episodes, the mean duration of myocardial ischemia was 25.4 ± 15 min. Intraoperative ischemia (four episodes) was detected in 4 patients, 3 in the thiopental-isoflurane group during induction and intubation and 1 in the propofol group during insertion of the hip prosthesis. The remaining 12 episodes occurred postoperatively: 3 during PACU recovery in 2 patients in the thiopental-isoflurane group and 1 in the propofol group, and 9 episodes on the ward, 5 in the propofol group, and 4 in the thiopental-isoflurane group.

Of 16 ischemic episodes, 11 (70%) were not associated with any hemodynamic changes. Myocardial ischemia was associated with hypertension and intubation in one patient in the thiopental-isoflurane group, with postoperative hypotension in the PACU in one patient in the thiopental-isoflurane group, and with tachycardia on the ward in two patients in the propofol group and in one in the thiopental-isoflurane group.

Postoperative 12-lead ECG and CPK-MB enzyme determinations did not detect any evidence of ischemia or myocardial infarction (MI) in either anesthetic group. No patient suffered from angina or MI during the convalescent course.

Recovery

Patient recovery following propofol infusion anesthesia was significantly faster than that following the thiopental-isoflurane regimen. However, earlier recovery from propofol anesthesia did not result in earlier discharge from the PACU [ie, discharge time for the propofol group was 116.4 ± 28 minutes compared with 131.6 ± 44 minutes for the thiopental-isoflurane group (p = NS)]. Independent of anesthetic regimen, postanesthetic recovery was slower in patients who were at least 70 years of age.

Mental Alertness

There was no significant difference in time from discontinuation of N, O to extubation between the propofol group and the thiopental-isoflurane group (6.9 ± 2.5 min vs. 9.7 ± 2.5 min). Patients in the propofol group responded to verbal command, recovered mental orientation, and achieved maximum Aldrete scores of 10 at 4, 6, and 20 minutes (respectively) sooner than those in the thiopental-isoflurane group (p < 0.05) (Table 3). These differences in postanesthetic recovery were particularly noticeable in patients aged 70 years or greater.

On the ward, delirium was observed in three patients: 9 hours postoperatively in one patient in the thiopental-isoflurane group in whom it was associated with a transient episode of cerebral ischemia, which was detected clinically; on postoperative day two in one patient in the propofol group, and on postoperative day four in one patient in the thiopental-isoflurane group, in whom it was associated with pneumonia.

Side Effects

The incidence of postanesthetic nausea and vomiting was similar in the two study groups. In the PACU, nausea was detected in 5 patients in the propofol group (17%) and 7 patients in the thiopental-isoflurane group (25%), while vomiting occurred in 1 patient in the propofol group and 3 patients in the thiopental-isoflurane group (p = NS). On the ward, nausea persisted in 7 patients and vomiting in 4 patients, with no difference between the study groups.
Discussion

Our findings indicate that induction of anesthesia by slow propofol infusion is comparable to that of thiopental bolus induction in speed of induction and hemodynamic effect, suggesting that propofol induction by infusion may be a suitable alternative to conventional bolus induction.

Bolus administration of propofol for induction of anesthesia can produce hypotension, and elderly patients are at greatest risk.23 Propofol is known to diminish cardiac output and systemic vascular resistance stemming from vasodilatation and negative inotropic effects.24 In the elderly, this hypotensive response is often exaggerated15,25 because of a reduced initial volume of distribution.13 When used in equipotent dosage,2,3,26 bolus administration of propofol causes a greater degree of cardiovascular depression than does conventional thiopental induction.27

However, induction of anesthesia by propofol infusion in our unpremedicated, elderly patients did not decrease BP significantly or produce bradycardia. The maximum decline in SBP immediately after induction by propofol infusion and thiopental bolus administration was comparable (-8.3 ± 5.5% vs. -6.3 ± 3.4%). Furthermore, cardiovascular sympathetic responses to laryngoscopy and intubation were better attenuated by propofol infusion than by thiopental bolus.

Minimal hemodynamic changes after propofol induction by infusion likely result from several important factors. First, the total dose for induction was 1.6 mg/kg, similar to the recommended dose reduction for bolus administration in elderly patients. Second, the rate of propofol injection influences the magnitude of changes in BP and HR.11,12 and our infusion rate of 0.75 mg/kg/min (=300 ml/hr) was relatively slow. Third, slower induction with propofol infusion permits the clinician more time to observe for the anesthetic endpoint of loss of eyelash reflex, thereby reducing the risk of over- or under-dosing associated with the administration of an arbitrary bolus dose.

Some preliminary studies11,12 also have identified several advantages of propofol infusion as an alternative induction technique. First, slow rate of infusion (300 ml/hr) was found to result in lower plasma propofol concentration and less hemodynamic derangement at the end of induction than with a faster rate (1,200 ml/hr).11,12 In the present study, when propofol was infused at 300 ml/hr, we observed an even smaller decrease in SBP (8.5 ± 5.5%) than in an earlier study (19%).11 The greater degree of hemodynamic stability in our patients may have resulted from prehydration with 10 ml/kg of crystalloid solution prior to induction.

Second, a slower rate of propofol infusion produces less slowing of HR.11 Propofol is known to permit reduction in BP without compensatory tachycardia.28 Third, a slower rate of propofol administration reduces the amount of drug required to induce anesthesia. In one study of elderly patients, an infusion rate of 1,200 ml/hr required a dose of 2.5 mg/kg to achieve induction of anesthesia but a rate of 300 ml/hr required only 1.2 mg/kg.11 Similar rate-dependent induction phenomena also were observed in younger patients.12 The mechanisms responsible for the apparent relationship between anesthetic dose, rate of administration, and successful induction of anesthesia are not clear.

Our findings also demonstrate that the infusion of propofol for anesthesia results in more rapid recovery for elderly patients. All measured recovery outcomes, includ-
Despite earlier achievement of full Aldrete discharge scores in our patients undergoing the propofol infusion regimen, PACU discharge time did not differ between our two anesthetic groups. This finding suggests that patient discharge from the PACU may not have followed Aldrete's postanesthetic discharge criteria as closely as desired. Also, PACU discharge may have been delayed by other circumstances independent of postanesthetic recovery.

Hypotensive episodes at the time of induction of anesthesia may precipitate myocardial ischemia in elderly patients with preexisting CAD. Although our technique of slower anesthetic induction by propofol infusion reliably preserved hemodynamic stability, the occurrence of perioperative myocardial ischemia did not differ by anesthetic regimen, and the timing of the ischemic episodes did not correlate with hypotensive events. This is consistent with findings of earlier studies in which propofol-induced hypotension in patients with known CAD was compensated by a similar reduction in myocardial O₂ consumption, resulting in little hypotension-related myocardial ischemia or increased myocardial lactate production.²⁹

We have compared propofol induction by infusion with thiopental bolus induction in this study, realizing that there are distinct pharmacokinetic differences resulting from these two techniques of anesthetic induction. The observed difference in the sympathetic responses to laryngoscopy and intubation between the two induction techniques was likely the result of differences in drug redistribution. Patients receiving propofol infusion likely benefited from a sustained blood anesthetic concentration during laryngoscopy and intubation, in contrast to the rapid redistribution and decline in blood concentration of thiopental in the other group. Thus, pharmacokinetic, rather than pharmacodynamic, differences likely explain the difference in response to laryngoscopy and intubation in our two anesthetic groups.

In summary, we found that induction of anesthesia by propofol infusion in elderly patients minimized the risks of hypotension and bradycardia and produced greater attenuation of cardiovascular sympathetic response to intubation than did thiopental bolus induction. Our results suggest that the infusion technique may be a suitable alternative to bolus administration when propofol is to be used.

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<th>Table 3. Postanesthetic Recovery Data</th>
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<td>Time to full Aldrete score of 10 (min)</td>
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<td>Time to PACU discharge (min)</td>
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Note: Values are expressed as the mean ± SD.

*P < 0.01 between propofol and thiopental-isoflurane groups.
†P < 0.03 between propofol and thiopental-isoflurane groups.
used for anesthesia. Finally, induction and maintenance of anesthesia by propofol infusion resulted in more rapid recovery in our elderly patients than thiopental-isoflurane anesthesia.

References


