Original Article

Comparing the effects of three different additional doses of propofol infusion on intubation condition and hemodynamic changes during general anesthesia under elective surgery: A randomized, placebo-controlled, double blind clinical trial

Mohammadreza Safavi, Azim Honarmand, Golnaz Banisadr

Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Laryngoscopy and endotracheal intubation can induce unfavorable hemodynamic changes as propofol itself can induce hypotension. The aim of this study was to compare the effects of three different additional doses of propofol infusion on intubation conditions and hemodynamic changes occurred after intubation.

Materials and Methods: This double-blinded prospective study was performed on 140 patients aged 18-60 who received different additional doses of propofol and were randomly allocated into 4 groups as follows: A: Received additional dose of propofol 0.5 mg/kg infused after an initial dose 1.5 mg/kg. B: Received additional dose of propofol 1 mg/kg infused after an initial dose 1 mg/kg. C: Received additional dose of propofol 1.5 mg/kg after an initial dose 1 mg/kg. D: Received propofol 2 mg/kg as a bolus with no additional dose.

Results: Intubation conditions were acceptable in 91.4% of Group A patients, 94.2% of Group B patients, 97.1% of Group C patients and 68.5% of Group D patients. There were no significant differences in the mean of heart rate between four groups at any time before and after laryngoscopy. Mean arterial pressure (MAP) 3 min after laryngoscopy was significantly lower in Group D versus Group A ($P = 0.015$) while MAP was not different at any time between other groups.

Conclusion: Infusion of propofol 1.5 mg/kg added to initial bolus dose of propofol 1 mg/kg improves intubation conditions significantly without inducing hemodynamic changes.

Key Words: Hemodynamic, intubation conditions, laryngoscopy, propofol

Address for correspondence:
Prof. Azim Honarmand, Anesthesiology and Critical Care Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: honarmand@med.mui.ac.ir
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INTRODUCTION

High body uptake as well as rapid elimination makes propofol an excellent controllable intravenous hypnotic that is widely used for induction and maintenance of general anesthesia.[1] Earlier studies have described the effects of propofol on intubation conditions. Propofol may improve intubation conditions in a dose-dependent manner.[2] Kwon *et al*.[3] showed

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that the administration of additional dose of propofol (0.5 mg/kg) prior to intubation may improve intubation conditions significantly without affecting hemodynamic variables. Above study described the effects of only one additional dose of propofol on intubation conditions and that was, as a bolus. Therefore, we designed this study to compare three different additional doses of propofol infusion on intubation conditions and hemodynamic changes before and after laryngoscopy.

MATERIALS AND METHODS

After obtaining institutional approval and written informed consents, 140 American Society of Anesthesiologists (ASA), physical status I, II and patients aged 18-60 years, scheduled for elective surgery, were enrolled in a prospective randomized double-blind study. Other inclusion criteria included patients with normal airway and body mass index less than 27.5 kg/m^2 and more than 18.5 kg/m^2. Exclusion criteria included sensitivity to propofol and anesthesia with techniques, different from the protocol of this study.

Patients were randomly allocated by using random allocation software into one of four groups as follows:

A. Received additional dose of propofol 0.5 mg/kg infused after an initial dose 1.5 mg/kg
B. Received additional dose of propofol 1 mg/kg infused after an initial dose 1 mg/kg
C. Received additional dose of propofol 1.5 mg/kg after an initial dose 1 mg/kg
D. Received propofol 2 mg/kg as a bolus with no additional dose.

The randomized process and the identity of the study drugs were blinded from the patients, the participating Anesthesiologist during surgery and the investigators who collected the post-operative data.

In all groups, fentanyl 2 μg/kg was administered intravenously prior to induction. After the loss of consciousness was confirmed, atracurium 0.6 mg/kg was administered within 10 s. In each group, additional dose of propofol was infused within 90 s by infusion pump. Laryngoscopy was performed 2 min after atracurium administration.

Heart rate (HR) and mean arterial pressure (MAP) were examined and recorded at pre-induction, immediately prior to laryngoscopy, 1, 3, 5 and 10 min after laryngoscopy. If MAP was less than 60 mmHg, 5 mg ephedrine was given. If HR was less than 50 bpm, 0.5 mg atropine was administered. For blinding purposes, person who was responsible for administration of induction drugs, was varied from whom collected data. Side-effects included, hypotension (MAP <60 mmHg), bradycardia (HR <50 bmp), tachycardia (HR >100 bpm), laryngospasm, bronchospasm and cyanosis were examined and recorded. If intubation conditions were unacceptable (poor or impossible), atracurium 0.2 mg/kg was administered and then endotracheal intubation was performed. Intubation conditions were examined and categorized by Magorian *et al*.[4] scoring system as follows: Excellent = when jaw is relaxed, vocal cords are abducted and immobile and there is no diaphragmatic movement. Good = when the jaw is relaxed, vocal cords are abducted and immobile, but there is some diaphragmatic movement. Poor = when the jaw is relaxed, but vocal cords moving and coughing or bucking happens. Impossible: When the jaw is not relaxed and vocal cords are closed. We considered excellent and good as acceptable intubation conditions and poor and impossible as unacceptable intubation conditions. We categorized laryngoscopy grades by Cormack and Lehane[5] classification as one of the following: Grade 1 = most of the glottis opening can be seen; Grade 2 = only the posterior portion of the glottis or only arytenoid cartilages are visible; Grade 3 = only the epiglottis but no portion of glottis is visible; Grade 4 = Neither the glottis nor the epiglottis can be seen. Duration of performing laryngoscopy and endotracheal intubation was also recorded. A power analysis indicated that a sample size of 35 in each group was required to detect a difference in the numbers of patients with adequate intubation conditions of at least 20% among the four groups (power 80%, α error = 0.05).

Data were analyzed using the statistical package for the social sciences (version 16) system. Qualitative data were analyzed by Chi-square test. We used analysis of variance to evaluate mean of quantitative data among four groups. Data were presented as mean ± SD or numbers. $P < 0.05$ was considered as significant.

RESULTS

A total of 140 patients were enrolled in the study. The flowchart of randomized patients is shown in Figure 1. No patient was excluded from the study. There were no significant differences in demographic data and duration of laryngoscopy between four groups [Table 1]. There was no significant difference in laryngoscopy grades between four groups [Table 2]. Intubation conditions were acceptable in 91.4% of Group A patients, 94.2% of Group B patients, 97.1% of Group C patients and 68.5% of Group D patients. Intubation conditions were significantly better in group C than other groups ($P < 0.05$). Furthermore, the number of patients

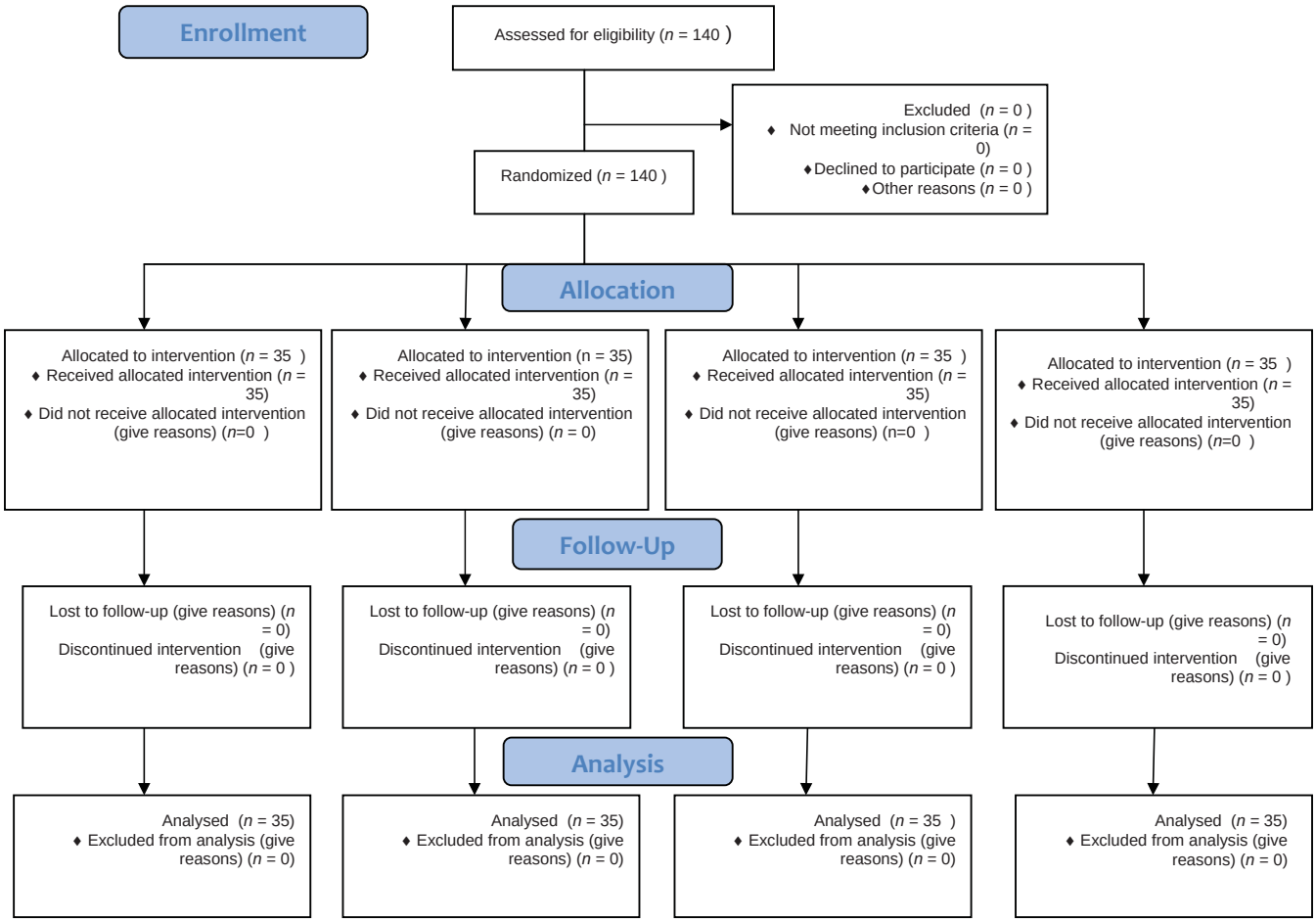

Figure 1: Consort flowchart

Table 1: Demographic data, duration of laryngoscopy and administration of added doses of atracurium in four groups

Variables	Group (*n*=35)				*P* value
	A	B	C	D	
Gender (M/F)	23/12	25/10	27/8	20/15	0.32
Age (years)	29.2±10.9	32.9±12.9	31.2±5.9	34±11.4	0.251
Height (cm)	168.9±7	168.8±8.2	167.5±5.2	168.9±5	0.745
Weight (kg)	71.5±14.3	74.5±13.1	72.7±5.7	70.5±8.4	0.457
ASA (I/II)	33/2	30/5	32/4	30/5	0.638
Duration of laryngoscopy (s)	11.7±8.8	12.1±9.2	11.7±6.7	11.7±7.3	0.947
Added atracurium (mg)	15.67±3.2	15±4.2	16	14.73±2.2	0.925

Data are shown in mean±SD. No significant difference was noted between four groups. ASA: American Society of Anesthesiologists physical status, A: Received additional dose of propofol 0.5 mg/kg infused after an initial dose 1.5 mg/kg, B: Received additional dose of propofol 1 mg/kg infused after an initial dose 1 mg/kg, C: Received additional dose of propofol 1.5 mg/kg after an initial dose 1 mg/kg, D: Received propofol 2 mg/kg as a bolus with no additional dose, SD: Standard deviation

Table 2: Laryngoscopy grades among the study groups

Grade	Group (*n*=35)				*P* value
	A	B	C	D	
1	9	18	13	16	0.152*
2	24	13	16	15	
3	2	4	6	4	
4	0	0	0	0	

Data are expressed in numbers. *P>0.05 between groups. A: Received additional dose of propofol 0.5 mg/kg infused after an initial dose 1.5 mg/kg, B: Received additional dose of propofol 1 mg/kg infused after an initial dose 1 mg/kg, C: Received additional dose of propofol 1.5 mg/kg after an initial dose 1 mg/kg, D: Received propofol 2 mg/kg as a bolus with no additional dose

with excellent intubation conditions was significantly higher in Group C (71.4%) than Group A (31.4%) and Group B (37.1%) and Group D (11.4%) ($P < 0.05$). One case of impossible intubation condition was reported in group D. After administration of atracurium, intubation was performed [Table 3]. No significant difference was noted in the mean of added doses of atracurium between four groups [Table 1]. There were no significant differences in the mean of heart rate between four groups, at any time before and after laryngoscopy [$P > 0.05$, Figure 2]. MAP 3 min after laryngoscopy, was significantly lower in Group D versus Group A ($P = 0.015$), while MAP did not differ at any time between other groups [$P > 0.05$, Figure 3]. One patient in Group A and three patients in Group C had bradycardia (HR <50 bpm) and required atropine ($P > 0.05$). Two patients in Group A and four patients in Group D had hypotension (MAP < 60 mmHg) and required

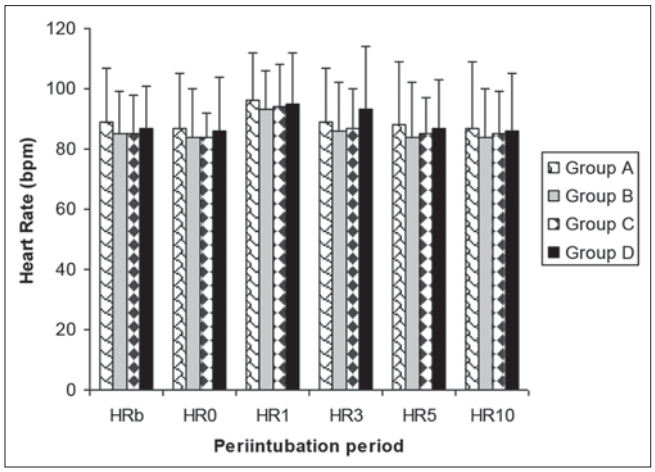

Figure 2: Heart rate (HR) among the four groups at peri-intubation periods. Data are shown in mean (±SD). $P > 0.05$ between groups. A: Received additional dose of propofol 0.5 mg/kg infused after an initial dose 1.5 mg/kg. B: Received additional dose of propofol 1 mg/kg infused after an initial dose 1 mg/kg. C: Received additional dose of propofol 1.5 mg/kg after an initial dose 1 mg/kg. D: Received propofol 2 mg/kg as a bolus with no additional dose. HRb: HR (bpm) before induction. HR0: HR (bpm) immediately before laryngoscopy. HR1: HR (bpm) 1 min after laryngoscopy. HR3: HR (bpm) 3 min after laryngoscopy. HR5: HR (bpm) 5 min after laryngoscopy. HR10: HR (bpm) 10 min after laryngoscopy

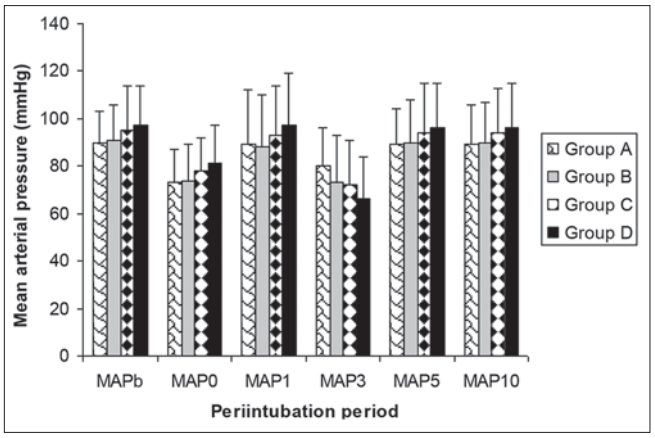

Figure 3: Mean arterial pressure (MAP) among the four groups at peri-intubation periods. Data are shown in mean (±SD). *$P = 0.015$ in Group D versus Group A at 3 min after laryngoscopy. $P > 0.05$ between other groups at any time. A: Received additional dose of propofol 0.5 mg/kg infused after an initial dose 1.5 mg/kg. B: Received additional dose of propofol 1 mg/kg infused after an initial dose 1 mg/kg. C: Received additional dose of propofol 1.5 mg/kg after an initial dose 1 mg/kg. D: Received propofol 2 mg/kg as a bolus with no additional dose. MAPb: MAP (mmHg) before induction. MAP0: MAP (mmHg) immediately before laryngoscopy. MAP1: MAP (mmHg) 1 min after laryngoscopy. MAP3: MAP (mmHg) 3 min after laryngoscopy. MAP5: MAP (mmHg) 5 min after laryngoscopy. MAP10: MAP (mmHg) 10 min after laryngoscopy

Table 3: Intubation conditions among the study groups

Intubation conditions	Group (*n*=35)			
	A	B	C	D
Excellent	11 (31.4)	13 (37.1)	25 (71.4)	4 (11.4)
Good	21 (60)	20 (57.1)	9 (25.7)	20 (57.1)
Acceptable	32 (91.4)	33 (94.2)	34 (97.1)**	24 (68.5)*
Poor	3 (8.6)	2 (5.7)	1 (2.9)	10 (28.6)
Impossible	0	0	0	1 (2.9)
Unacceptable	3 (8.6)	2 (5.7)	1 (2.9)	11 (31.5)

Data are expressed in numbers (percentage). *P<0.05 in Groups A, B and C versus Group D. **P<0.05 in Group C versus Groups A, B and D. A: Received additional dose of propofol 0.5 mg/kg infused after an initial dose 1.5 mg/kg, B: Received additional dose of propofol 1 mg/kg infused after an initial dose 1 mg/kg, C: Received additional dose of propofol 1.5 mg/kg after an initial dose 1 mg/kg, D: Received propofol 2 mg/kg as a bolus with no additional dose

Table 4: The incidence of complications in four groups

Variables	Group (*n*=35)			
	A	B	C	D
Bradycardia (HR <50 bpm)	1 (2.9)	0	0	3 (8.6)
Tachycardia (HR >100 bpm)	7 (20)	6 (17.1)	5 (14.3)	6 (17.1)
Hypotension (MAP <60 mmHg)	2 (5.7)	0	0	4 (11.4)
Bronchospasm	0	0	0	0
Laryngospasm	0	0	0	0
Cyanosis	0	0	0	0

Data are expressed in numbers (percentage). P>0.05 between groups. A: Received additional dose of propofol 0.5 mg/kg infused after an initial dose 1.5 mg/kg, B: Received additional dose of propofol 1 mg/kg infused after an initial dose 1 mg/kg, C: Received additional dose of propofol 1.5 mg/kg after an initial dose 1 mg/kg, D: Received propofol 2 mg/kg as a bolus with no additional dose, HR: Heart rate, MAP: Mean arterial pressure

ephedrine ($P > 0.05$). No laryngospasm, bronchospasm and cyanosis were noted in any of the study groups. As a result there were no significant differences in side-effects between four groups [$P > 0.05$, Table 4].

DISCUSSIONS

Endotracheal intubation is a rapid and safe way to achieve all the goals of airway management; although, it can be associated with complications that sometimes threaten patient's health.[6] Complications such as bronchospasm[7] and laryngospasm[6] may result from attempted intubation under light anesthesia, that can lead to hypoventilation and hypoxia. Difficult airway and failed intubation include a range of difficult mask ventilation, difficult laryngoscopy, difficult intubation and failed intubation. The most dangerous situation is a cannot ventilate intubate situation[8,9] that occurs in about 1 in 10,000 anesthetics and oxygenation failure can lead to death or hypoxic brain damage. Laryngoscopy and endotracheal intubation induce sympathetic reflex stimulation with raised catecholamine plasma levels, that may lead to hypertension, tachycardia, myocardial ischemia, ventricular arrhythmias, intracranial or intraocular hypertension.[10] This adverse autonomic response may be severe during a difficult intubation. Our study showed that infusion of propofol 1.5 mg/kg added to an initial bolus dose of propofol 1 mg/kg improves intubation conditions significantly without inducing hemodynamic changes. Recent studies have described

the effects of increasing doses of propofol on intubation conditions. Lieutaud *et al.*[11] found that increasing doses of propofol especially when used with a muscle relaxant improved intubation conditions significantly. In their study, 95% of patients who received propofol 2.5 mg/kg and atracurium 0.5 mg/kg, had clinically acceptable intubation conditions. Gore *et al.*[12] evaluated intubation conditions with different doses of propofol without muscle relaxant. They used different doses of propofol as 2, 2.5 and 3 mg/kg with fentanyl 2 μg/kg and lignocaine 1.5 mg/kg. They found that ideal intubation conditions without muscle relaxant can be achieved with propofol 3 mg/kg without significant hemodynamic changes. In this study, laryngoscopy was performed 7 min after fentanyl injection, as some authors have described that the peak action of fentanyl comes after 7 min.[13,14] However, in many studies as our study laryngoscopy was performed earlier. Kwon *et al.*[3] showed that the administration of additional dose of propofol (0.5 mg/kg) prior to intubation may improve intubation conditions significantly without inducing hypotension. They found that adding a booster of propofol, increases it's plasma concentration at intubation, thus it might augment intubation conditions. The muscle relaxing mechanisms of intravenous anesthetics, especially propofol, have been investigated in several studies.[15-18] Some authors have demonstrated a central (cortical and spinal cord) mechanisms to describe muscle relaxing properties of propofol. Dueck *et al.*[16] explained that propofol bolus administration impaired the central part of the motor system by decreasing in α-motor neuron excitability as shown by a decreased spinal F wave. Some authors have described a peripheral mechanism. Fujii *et al.*[17] used electromyography to show that subhypnotic and anesthetic doses of propofol decrease diaphragmatic contractility in dogs. Haeseler *et al.*[18] demonstrated that propofol inhibited human skeletal muscle sodium channels in a voltage-dependent manner. Several recent studies have described the effects of propofol on hemodynamic status.[19,20] Propofol leads to hypotension by peripheral vasodilation and negative inotropic and chronotropic properties, especially in patients with cardiovascular diseases, following its rapid administration.[21] Moreover, propofol's effect on cortical vagal tone can result in bradycardia and conductive disturbances.[22,23] Chang *et al.*[24] showed that propofol produces vasodilation by an endothelium-independent mechanism and may act as a Ca^{2+} blocker, similar to that of Ca^{2+} channel blocker, verapamil. In our study, we found that infusion of the increased doses of propofol did not affect the hemodynamic status. MAP 3 min after laryngoscopy was significantly lower in Group D than Group A. we think that the higher dose of propofol at induction might cause that. It's important to note that our study had limitations. We just studied on patients with ASA I and ASA II and not younger than 18 years or older than 60 years. Moreover, we didn't investigate the effects of combination of propofol with sedatives on intubation conditions. Furthermore, we didn't measure the plasma concentration of propofol in the study groups.

CONCLUSIONS

Infusion of propofol 1.5 mg/kg added to an initial bolus dose of propofol 1 mg/kg improves intubation conditions significantly without inducing hemodynamic changes or side-effects.

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