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## Anesthetic recovery and hemodynamic effects of continuous thiopental infusion versus halothane for maintenance anesthesia in patients undergoing ocular surgery<sup>1</sup>

Recuperação anestésica e efeitos hemodinâmicos da infusão contínua de tiopental versus halotano na manutenção da anestesia em pacientes submetidos à cirurgia ocular.

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### ABSTRACT

**Purpose:** To investigate anesthesia recovery and hemodynamic status in patients under thiopental infusion or halothane maintenance anesthesia undergoing ocular surgery. **Methods:** Fifty-nine voluntary patients undergoing ocular surgery in Farabi hospital were allocated to one of two maintenance anesthesia groups: inhaled halothane, 0.8 to 1 per cent, (group I, n=37) and thiopental infusion, 10 to 12 mg/kg/hour, (group II, n=22). Hemodynamic parameters were recorded at the time of patient entrance to the operation room and at the 1, 2, 5, 10, 15, 20, 25, 30, 35, and 40 minutes following anesthesia. Anesthesia recovery variables were also compared between the two groups. **Results:** In group I, arterial blood pressure at 10 to 40 min and heart rate at 1 and 25 min after the administration of anesthetics were significantly lower when compared with group II ( $W^2 = 25.10$ ,  $p = 0.005$ ). Arterial oxygen saturation was similar in the two groups over the whole points of time. The time intervals between the end of surgery and beginning of the first body movements and respiratory efforts were significantly longer in group received halothane ( $p < 0.001$ ). **Conclusions:** Continuous infusion of thiopental can be applied effectively and safely for maintenance of anesthesia. In comparison with halothane, it is associated with lower changes of intraoperative hemodynamics and faster anesthesia recovery.

**Key words:** Thiopental. Halothane. Anesthesia Recovery Period. Hemodynamic. Eye. Surgery.

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### RESUMO

**Objetivo:** Investigar a recuperação anestésica e as condições hemodinâmicas em pacientes submetidos a infusão de tiopental ou halotano na manutenção da anestesia na cirurgia ocular. **Métodos:** Cinquenta e nove voluntários submetidos a cirurgia ocular no Hospital Farabi foram distribuídos em dois grupos de manutenção anestésica: Grupo I (n=37) inalação halotano, 0,8 a 1% e Grupo II (n=22) infusão de tiopental, 10 a 12 mg/kg/hora. Foram registrados parâmetros hemodinâmicos da entrada dos pacientes na sala operatória até 1, 2, 5, 10, 15, 20, 25, 30, 35 e 40 minutos durante a anestesia. Variáveis de recuperação anestésica foram também comparados entre ambos os grupos. **Resultados:** No Grupo I a pressão arterial nos 10 a 40 minutos e avaliação cardíaca em um e 25 minutos após a administração dos anestésicos foram significantes mais baixos comparados com o Grupo II ( $W^2=25.10$ ,  $p=0.005$ ). A saturação de oxigênio foi similar nos dois grupos durante todos procedimentos. Os intervalos de tempo entre o final da cirurgia e início dos primeiros movimentos e a respiração foram significativamente mais prolongados no grupo que recebeu halotano ( $p < 0.001$ ). **Conclusões:** A infusão contínua de tiopental pode ser aplicado efetivamente e com segurança na manutenção da anestesia. Em comparação com halotano as mudanças hemodinâmicas foram menores e a recuperação anestésica mais rápida.

**Descritores:** Tiopental. Halotano. Período de Recuperação da Anestesia. Hemodinâmica. Olho. Cirurgia.

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## Introduction

Selection of the best anesthetic protocol with minimized complications is quite challenging and much scientific efforts have been focused on qualifying anesthesia. The use of volatile and induction agents can lead to hemodynamic alterations and serious cardiovascular and respiratory complications that have been documented in several animal models<sup>1</sup>. These side effects have been more marked with some agents such as halothane and thiopental. In some studies, it has been shown that the halothane could induce a profound alteration in heart and respiratory rates and abnormal cardiac rhythms included ventricular fibrillation, ventricular bigeminy, and multifocal ventricular rhythms were occurred by the use of this inhalational agent<sup>1-4</sup>. Furthermore, the changes in both systemic and cerebral hemodynamics have been shown in the patients undergoing general anesthesia by using thiopental<sup>5-7</sup>.

Although a relatively high incidence of cardiac arrhythmias and hemodynamic alterations during halothane and thiopental anesthesia has been reported in animal models, these changes have not been clearly investigated in humans. Moreover, since these two agents are used extensively in general anesthesia of patients undergoing various types of surgeries, it appears that a more detailed investigation in surgical patients is needed. There are a few reports to examine the continuous intravenous (IV) infusion of thiopental for maintenance anesthesia. The purpose of the present study was to compare the anesthesia recovery and hemodynamic status in patients under IV infusion thiopental versus halothane maintenance anesthesia undergoing ocular surgery.

## Methods

In a prospective clinical trial study, 59 voluntary patients of ASA grade 1 and 2 aged 22-86 years old with ocular and candidate for surgery in Farabi Hospital, Tehran, Iran were included. The investigation was approved by the Educational Hospital Ethics Committee, governing the participation of human subjects in research at the Tehran University of Medical Sciences, according to the principles outlined in the Declaration of Helsinki. The procedure and type of anesthetics were explained to the patients, and written informed consents were obtained from all the patients before induction of anesthesia. The participants with the history of cardiovascular disease, allergy to barbiturates, acute alternative porphyria, respiratory disorders, persistent asthma, Addison's disease, liver diseases, renal failure, myxedema, severe anemia, or myasthenia gravis were excluded. All patients

were given an intravenous injection of fentanyl (1.5 µg/kg), diazepam (0.1 mg/kg), 5 minutes before anesthesia induction. All patients underwent induction of anesthesia with a single bolus IV thiopental (4 to 6 mg/kg) and oxygen. After evaluating the effect of premedication, patients were randomly allocated to receive maintenance anesthesia by using either inhaled halothane (group I, n=37) after the tracheal intubation or continuous infusion of thiopental (group II, n=22) immediately after the anesthesia induction. Endotracheal intubation was facilitated with atracurium (0.5-0.7 mg/kg IV, maximum dose of 2.5 mg) and the mechanical ventilation was set at a rate of 12 per min and a volume of 10 ml/kg. Upon completion of surgery, the neuromuscular block was antagonized with neostigmine (80 µg/kg, maximum dose of 2.5 mg) and atropine (40 µg/kg).

In group I, inhaled concentration of halothane was set at 0.8% to 1%. The group II was given thiopental infusion of 10 to 12 mg/kg/hour by using infusion pump. This infusion rate was maintained at a fix value during operation. Halothane was intraoperatively inspired with similar concentration. The doses of the halothane inhalation and thiopental infusion were chosen based on the clinical experience of the anesthetist of the Ophthalmology Surgery Hospital.

Hemodynamic parameters including systolic blood pressure, heart rate, and arterial oxygen saturation, were recorded at the time of patient entrance to the operation room and at the 1, 2, 5, 10, 15, 20, 25, 30, 35, and 40 minutes after the induction of anesthesia. Anesthesia recovery parameters were compared between the two groups. For this assessment, the time intervals between the end of surgery and the beginning of the first body movements, the first respiratory efforts, extubation, and patients' transferring to recovery room were recorded and examined. The depth of anesthesia was objectively and subjectively evaluated during the anesthesia and recovery period, respectively. The patients' movement and hemodynamics were considered for the objective assessment of the anesthesia. In the recovery room, all the patients were asked about the any sensation and sound during the general anesthesia.

We calculated a sample size so that a between-group mean difference in recovery time would permit a two-tailed Type I error rate of  $\alpha=0.05$  with a power of 69%. This analysis indicated that a sample size of at least 20 patients per group was necessary. After randomization of the patients who fulfilled the inclusion criteria, 59 patients who had the complete records for the intraoperative parameters and anesthesia recovery were selected.

Numerical variables were presented as mean  $\pm$  SD, while categorized variables were summarized by percentages.

Continuous variables were compared using the Student's t test or nonparametric Mann-Whitney U test whenever the data did not appear to have normal distributions, and categorical variables were compared using chi-square or Fisher's exact test, as required. Modeling the mean response over time was the main feature of analysis we followed to deal with the longitudinal data. In other words, since all individuals were measured at the same set of occasions, we performed separate Analyzing Response Profiles<sup>8</sup> using Proc Mixed in SAS to compare blood pressure, heart rate, and arterial oxygen saturation across the two groups. Halothane group and the time of patients' entrance to the operation room were considered as the reference points. Model parameters were estimated using Generalized Least Squares (GLS) estimator. Since Maximum Likelihood (ML) estimate of covariance matrix has well-known bias in finite samples, parameters of covariance matrix were estimated using Restricted Maximum Likelihood (REML) estimation. The type of covariance matrix was specified as unstructured, since we had no prior knowledge concerning the main feature of correlation type among responses across the time. For univariate analysis, the statistical software SPSS version 13.0 for windows (SPSS Inc., Chicago, IL) and for analyzing response profiles, the statistical package SAS version 9.1 for windows (SAS Institute Inc., Cary, NC, USA) were used. All p values were 2-tailed, with statistical significance defined by  $p \leq 0.05$ .

## Results

Demographic characteristics and medical history of the patients who received thiopental and halothane are shown in Table 1.

**TABLE 1** - Demographic characteristics and medical data of the patients received thiopental and halothane.

	<i>Thiopental group (n=22)</i>	<i>Halothane group (n=37)</i>	<i>P-value</i>
<b>Baseline characteristics:</b>			
Male gender	43.2	31.8	0.384
Age (year)	65.5±12.7	65.5±12.8	0.980
Weight (kg)	65.4±12.8	66.6±12.3	0.726
Hypertension	32.4	13.6	0.109
Diabetes mellitus	13.5	0.0	0.146
Substance abuse	5.4	0.0	0.524

Data are presented as mean ± SD (for continuous variables) or percentages (for categorical variables)  
 $p \leq 0.05$  from two-sided tests was considered statistically significant

Preoperative patient variables did not differ significantly with respect to gender, age, weight, and the previous histories of hypertension and diabetes mellitus. The depth of anesthesia was similar between groups. Also, the frequencies of current cigarette smoking and opium addiction were similar in the two groups.

In terms of hemodynamic parameters, there were no significant differences in the mean of systolic blood pressure at the time of patients' entrance to the operation room and in time points of one minute and five minutes after the administration of anesthetics; however, blood pressures were significantly appeared lower in halothane group across the other points if time (Table 2).

**TABLE 2** - Comparison of blood pressure between the patients received thiopental and halothane.

<i>Time after anesthesia</i>	<i>Systolic blood pressure</i>		
	<i>Thiopental group (n=22)</i>	<i>Halothane group (n=37)</i>	<i>P value</i>
<b>Minute 0</b>	154.1±34.5	146.4±33.2	0.405
<b>Minute 1</b>	126.2±47.2	105.0±28.9	0.062
<b>Minute 2</b>	112.8±38.1	93.0±27.0	0.036
<b>Minute 5</b>	102.4±31.1	89.8±27.0	0.118
<b>Minute 10</b>	110.3±27.3	94.1±26.8	0.031
<b>Minute 15</b>	118.0±32.2	93.9±24.7	0.004
<b>Minute 20</b>	125.0±32.6	97.7±24.5	0.001
<b>Minute 25</b>	123.5±28.4	100.9±15.1	<0.001
<b>Minute 30</b>	132.0±30.9	108.2±17.4	<0.001
<b>Minute 35</b>	129.3±17.9	110.9±18.9	<0.001
<b>Minute 40</b>	133.5±15.9	125.9±8.5	0.043

Data are presented as mean ± SD  
 $p \leq 0.05$  from two-sided tests was considered statistically significant

Also, two studied groups had similar mean heart rate at the time of patients' entrance to the operation room, but heart rates were significantly lower in halothane group over the time points of one minute through twenty five minutes after the administration of anesthetics (Table 3).

**TABLE 3** - Comparison of heart rate between the patients received thiopental and halothane.

Time after anesthesia	Heart rate		P value
	Thiopental group (n=22)	Halothane group (n=37)	
Minute 0	78.2±16.6	70.9±11.5	0.074
Minute 1	86.8±22.5	71.3±16.4	0.007
Minute 2	82.5±21.3	69.9±16.4	0.020
Minute 5	79.1±17.7	64.7±15.3	0.002
Minute 10	75.2±15.3	62.6±10.7	0.001
Minute 15	73.1±12.5	64.9±14.9	0.026
Minute 20	71.2±12.3	63.3±13.0	0.023
Minute 25	70.4±12.0	64.0±8.2	0.032
Minute 30	69.6±12.5	65.7±7.8	0.150
Minute 35	67.2±11.2	63.0±5.2	0.107
Minute 40	65.9±9.8	65.6±4.6	0.919

Data are presented as mean ± SD  
 p ≤ 0.05 from two-sided tests was considered statistically significant

Arterial oxygen saturation was followed a similar pattern in the two groups across the whole time points (Table 4).

**TABLE 4** - Comparison of arterial oxygen saturation between the patients received thiopental and halothane.

Time after anesthesia	Arterial oxygen saturation		P-value
	Thiopental group (n=22)	Halothane group (n=37)	
Minute 0	95.8±2.7	95.6±3.4	0.768
Minute 1	98.6±1.1	98.0±1.9	0.170
Minute 2	98.4±1.0	97.9±2.1	0.194
Minute 5	98.5±0.9	98.3±1.2	0.342
Minute 10	98.4±1.0	98.4±1.1	0.931
Minute 15	98.6±0.9	98.5±0.9	0.754
Minute 20	98.7±0.9	98.5±1.0	0.274
Minute 25	98.8±0.9	98.6±0.9	0.362
Minute 30	98.8±0.9	98.8±0.8	0.866
Minute 35	99.0±0.7	98.9±0.6	0.731
Minute 40	98.1±6.5	98.9±0.6	0.540

Data are presented as mean ± SD  
 p ≤ 0.05 from two-sided tests was considered statistically significant

Postoperative outcomes of the patients in the two studied groups are shown in Table 5.

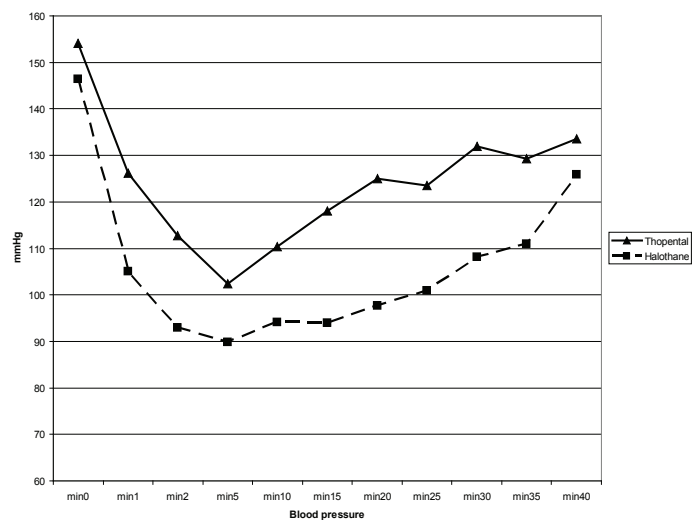
**TABLE 5** - Postoperative outcome of the patients received thiopental and halothane.

Item	Thiopental group (n=22)	Halothane group (n=37)	P value
Time interval between the end of surgery and beginning of the first body movements (min)	2.09±1.18	5.55±2.48	<0.001
Time interval between the end of surgery and beginning of the first respiratory efforts (min)	5.24±2.52	8.96±3.51	<0.001
Time interval between the end of surgery and extubation (min)	5.04±2.49	10.52±4.28	<0.001
Time interval between the end of surgery and transferring to recovery (min)	6.04±2.58	17.09±11.16	<0.001
Arrhythmia (%)	5.4	0.0	0.524

Data are presented as mean ± SD (for continuous variables) or percentages (for categorical variable)  
 p ≤ 0.05 from two-sided tests was considered statistically significant

The time intervals between the end of surgery and beginning of the first body movements, the first respiratory efforts, extubation, and transferring to recovery were all longer in group received halothane than in thiopental group.

Wald tests of fixed effects based on an analysis of response profiles of the blood pressure, heart rate, and arterial oxygen saturation levels comparing the thiopental and halothane groups, showed that the patterns of change (interaction between drug and time) in blood pressure ( $W^2=14.39$ ,  $p=0.156$ ) and in oxygen saturation ( $W^2=9.23$ ,  $p=0.511$ ) from baseline were not statistically different between the groups, whereas the pattern of change in heart rate from baseline was not the same between groups ( $W^2=25.10$ ,  $p=0.005$ ) (Figures 1 to 3).



**FIGURE 1** - Blood pressure after the administration of thiopental and halothane.

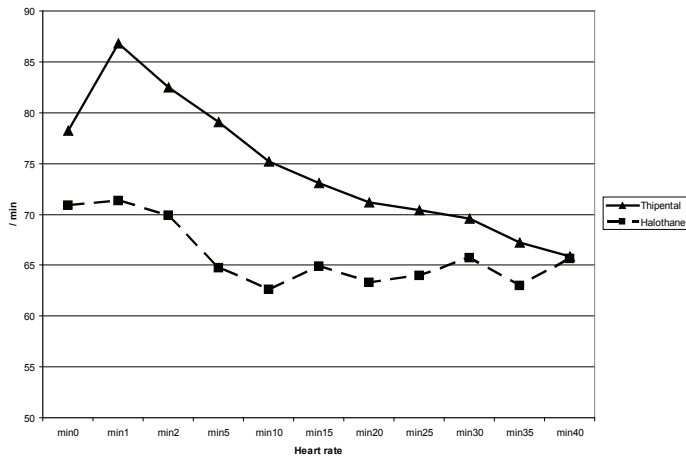


FIGURE 2 - Heart rate after the administration of thiopental and halothane.

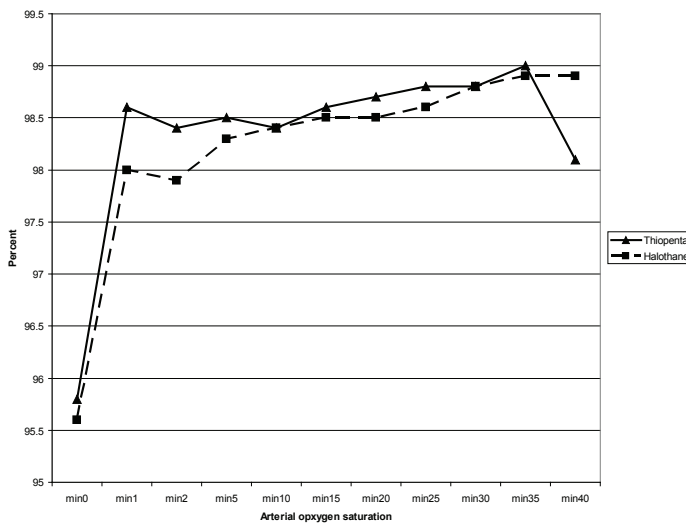


FIGURE 3 - Arterial O<sub>2</sub> saturation after the administration of thiopental and halothane.

Estimated regression coefficients and standard errors based on an analysis of response profiles comparing heart rate levels between the two groups revealed that the thiopental group had an additional increase in mean heart rate levels from the time of patients' entrance to the operation room to the time points of 20 minutes, when compared to halothane group. In contrast, the first group had an additional decrease in mean heart rate levels from 20 minutes through the last time point, in comparison with halothane group (Table 6).

TABLE 6 - Estimated regression coefficients and standard errors based on an analysis of response profiles of the heart rate levels comparison between thiopental and halothane groups.

P value	T value	Standard Error	Estimate	Time	Group	Variable
<0.0001	22.24	3.1857	70.8636			Intercept
0.0739	1.82	4.0228	7.3256		Thiopental	Group
.	.	.	0		Halothane	Group
.	.	.	0	0		Minute
0.9081	0.12	3.9181	0.4545	1		Minute
0.7678	-0.30	3.3708	-1.0000	2		Minute
0.0524	-1.98	3.0974	-6.1364	5		Minute
0.0070	-2.80	2.9421	-8.2273	10		Minute
0.0537	-1.97	3.0456	-6.0000	15		Minute
0.0117	-2.61	2.9124	-7.5909	20		Minute
0.0253	-2.30	2.9874	-6.8636	25		Minute
0.1127	-1.61	3.1883	-5.1364	30		Minute
0.0147	-2.52	3.1254	-7.8636	35		Minute
0.0808	-1.78	2.9409	-5.2273	40	Thiopental	Minute
.	.	.	0	0	Thiopental	Group×Time
0.1054	1.65	4.9476	8.1400	1	Thiopental	Group×Time
0.2161	1.25	4.2565	5.3243	2	Thiopental	Group×Time
0.0755	1.81	3.9113	7.0823	5	Thiopental	Group×Time
0.1670	1.40	3.7152	5.2002	10	Thiopental	Group×Time
0.8066	0.25	3.8459	0.9459	15	Thiopental	Group×Time
0.8787	0.15	3.6777	0.5639	20	Thiopental	Group×Time
0.7972	-0.26	3.7724	-0.9742	25	Thiopental	Group×Time
0.3940	-0.86	4.0261	-3.4582	30	Thiopental	Group×Time
0.4262	-0.80	3.9467	-3.1634	35	Thiopental	Group×Time
0.0610	-1.91	3.7173	-7.0971	40	Thiopental	Group×Time

p ≤ 0.05 from two-sided tests was considered statistically significant

### Discussion

Various types of anesthetic agents may influence and alter hemodynamic status, but these effects are different due to the type of these agents. In the present clinical trial study, we tried to examine the impact of continuous infusion of thiopental and inhaled halothane as maintenance anesthesia on operative hemodynamic status and also compare the time intervals between the end of surgery and the beginning of physical active responses for assessment of the recovery time. According to the obtained results, although systolic blood pressure and heart rate in patients who received thiopental was similar to those received halothane in baseline, these indices, in subsequent time points, were frequently lower in halothane group. Furthermore, postoperative movement, respiratory efforts, and transferring to recovery, following surgery, were initiated faster due to thiopental use compared to halothane. More effect of halothane on hemodynamic status in comparison with other anesthetic agents has been shown in the previous studies. Büch *et al.*<sup>9</sup> confirmed more decline of regional blood flow in many tissues induced by halothane. In a study by Goelz

*et al.*<sup>1</sup> it was indicated that both halothane and isoflurane altered heart rate and blood pressure; however, halothane induced a more profound alteration in heart rate and respiratory rate. In addition, in another study by Dedhia *et al.*<sup>2</sup> there was a notable reduction in the mean heart rate and systolic blood pressure in group received halothane at 30 seconds followed by a gradual fall. It has been shown that the halothane has a potential role on the conducting tissues of the ventricle and even its increased sensitivity to catecholamine blood pressure alterations and arrhythmias resulted primarily from its action on these tissues<sup>10</sup>. Moreover, it has been confirmed that halothane caused a significant and dose-dependent decrease in cardiac output and this reduction was dependent to halothane effects on antipyrine disposition profoundly affected by this anesthetic agent<sup>11</sup>.

Besides, alteration in hemodynamic status has been also caused by the use of thiopental and this effect can be mainly related to the change of cardiac parasympathetic tone<sup>12</sup>. However, the supportive roles of thiopental have been highlighted more than other agents. Kobayashi *et al.*<sup>13</sup> indicated that the thiopental had a greater suppressive effect on neuronal injury during identical duration of ischemic depolarization than halothane and propofol does, which can be due to its lower influence on hemodynamic alteration. Moreover, it seems that the effects of both anesthetic agents are dose-dependent and should be regulated on the basis of patient's age and clinical condition. It was previously attributed the mechanism for the 50-67% decrease in the required dose of thiopental for induction of anesthesia in aged human patients to a decrease in the initial distribution volume for thiopental<sup>14</sup>. It has been also concluded that the required dose of thiopental should be regulated by the evaluation of patient's blood gas situation so that the increase of thiopentone binding in human serum was more pronounced at pH 6 to 6.8 than at pH 7.4<sup>15</sup>. However, all patients with underlying disorders could cause blood gas alteration were excluded from the study.

In the present study, it was also found that the arterial oxygen saturation was similar between the two groups in all points of time and did not change within the time points of 1 to 40 minutes in both groups. However, previous findings indicated that the halothane and thiopental used at clinically relevant concentrations modulate the pulmonary SP-C mRNA content in animal models. It has been also confirmed that the volatile anesthetics can reduce surfactant phospholipid biosynthesis by rat alveolar type II cells<sup>16</sup>. However, respiratory effects of both agents should be more investigated in further human studies.

There are some potential limitations in interpreting these data. Our randomized clinical study was an open-label investigation,

necessitated by the various modes of drug administration and the differing physical appearances of the anesthetic and analgesic drugs. However, the personnel caring for study patients in the postoperative period were unaware of the anesthetic and analgesic drugs given intra-operatively and thus remained unbiased.

## Conclusions

Continuous infusion of thiopental can be applied effectively and safely for maintenance of anesthesia. In comparison with halothane, it is associated with lower changes of intraoperative hemodynamics and faster anesthesia recovery.

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