Original Article

A Comparative Study of the Effect of Anesthesia Induction with the Use of Four Drug Combinations Including "Propofol," "Etomidate-Propofol," "Thiopental," and "Midazolam-Thiopental" on Hemodynamic Changes during the Insertion of Laryngeal Mask in Eye Surgery

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Abstract

Background: This study aimed to compare the efficacies of four anesthetic induction drugs (thiopental, propofol, midazolam-thiopental, and etomidate-propofol) on cardiovascular response during laryngeal mask airway (LMA) placement in eye surgery. **Materials and Methods:** The present clinical trial study included 128 patients who were candidates for ophthalmic surgery in four groups. Patients in the first group were given a combination of midazolam (0.04 mg/kg) with thiopental (2.5 mg/kg) (Group T + M). We administered propofol alone (2.5 mg/kg) to patients in the second group (Group P). The third group received a combination of etomidate (0.1 mg/kg) with propofol (1 mg/kg) (ET + P group) and patients in the fourth group received thiopental drug (5 mg/kg) alone (Group T). Then, the stability of patients' hemodynamic parameters before anesthesia was evaluated and compared immediately after anesthesia, 1, 3, and 5 min after LMA placement. **Results:** There was no significant difference between the four groups in changes in oxygen saturation level ($P > 0.05$). Furthermore, the difference between decreased systolic blood pressure and diastolic blood pressure over time was not significant in 5 min in both Groups T + M and T ($P > 0.05$). In addition, the stability of these two groups was higher than the other two groups ($P < 0.05$) and the most unstable group was Group P. The changes pulse rate in the P group were significant ($P < 0.05$). **Conclusion:** According to the results of the current study, thiopental and Midazolam can be used as an effective induction compound to facilitate LMA insertion with higher hemodynamic stability compared to propofol alone, propofol and etomidate, and thiopental alone.

Keywords: *Etomidate, laryngeal mask, midazolam, ophthalmologic surgical procedures, propofol, thiopental*

Introduction

The management of airway and patient safety is one of the most important concerns of physicians so that a number of instruments and methods have been invented to achieve this aim.[1,2] Laryngeal mask airway (LMA) as a simple supraglottic device requires no direct laryngoscopy for placement.

Various methods have been introduced to insert LMA. However, there is thus far no standard induction method for anesthesia which guarantees LMA placement in a proper manner.[3,4]

One of the most dangerous times to begin the induction is when laryngoscopy and intubation is performing because it causes severe changes in blood pressure and heart rate.[5] This level of changes is not tolerable for all patients and may cause irreparable damage and increase the risk of death.[6]

One way to reduce hemodynamic changes is enough deep anesthesia induction with rapid-acting intravenous (IV) medications. It can provide an easy quick anesthesia in a short time.[5] Today, the most common anesthetic drugs for LMA placement are propofol and thiopental. These medications induce limited hemodynamic changes with an easy deep anesthesia. However, thiopental is not recommended for patients with asthma, who are not stable in terms of cardiovascular condition, patients with advanced cardiovascular problems,

How to cite this article: Shetabi H, Montazeri K, Ghoodjani Y. A Comparative study of the effect of anesthesia induction with the use of four drug combinations including "propofol," "etomidate-propofol," "thiopental," and "midazolam-thiopental" on hemodynamic changes during the insertion of laryngeal mask in eye surgery. Adv Biomed Res 2022;11:11.

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Received: 28 June 2020
Revised: 25 August 2020
Accepted: 27 October 2020
Published: 28 February 2022

Access this article online

Website: www.advbiores.net

DOI: 10.4103/abr.abr_152_20

Quick Response Code:

hypovolemic shock or porphyria.[7] On the other hand, the likelihood of increased blood pressure and heart rate followed by laryngoscopy and intubation when anesthesia is induced by propofol is lower than thiopental but dose-dependent propofol can reduce blood pressure. This issue may be accompanied by blood pressure reduction due to decreased blood flow and oxygenation in old patients and pregnant women.[8] Moreover, when propofol is administered alone to place LMA it can result in adverse complications such as coughing, gag reflex, and laryngospasm.[9,10]

Hence, lots of efforts have been made to use drugs or their combinations to reduce the level of hemodynamic instability to induce no risk to patients. Etomidate is an IV medication which can be used alone or in combination of other anesthetic drugs to induce anesthesia.[11] It is more popular for emergency intubation by maintaining hemodynamic stability and minimizing the debilitating effects of cardiopulmonary resuscitation.[12,13]

It is often administered to cardiac patients. In this group of patients the risk of cardiovascular instability after applying other IV anesthetics such as propofol or thiopental cannot be ignored. Etomidate has a rapid onset and emergence from anesthesia and no association with histamine release.[14] Moreover, it has sedative and hypnotic characteristics but no analgesic effects.[15]

Benzodiazepines are also one of the most commonly used medications in anesthesia of which one of the most widely used is midazolam. This short-acting drug is associated with water-soluble properties, rapid and painless effect, or thrombophlebitis at the time of injection and is associated with low hemodynamic changes.[16] In addition to sedative effects, this drug has beneficial effects such as futuristic forgetfulness, minimal weakening of ventilation and circulatory system, anticonvulsants, rare physical dependence and allergic reactions, and having a selective antagonist (flumazenil).[17,18] Numerous studies have shown that midazolam compared to thiopental in people with underlying disease has better hemodynamic stability.[7,19,20]

Therefore, anesthetic compounds may be suitable for LMA placement. To this end, the main aim of the present study was to compare the efficacy of four different anesthesia induction methods (propofol [P], propofol + etomidate [ET], thiopental [T] and thiopental + midazolam [T + M]) on cardiovascular response at the time of LMA placement in eye surgery.

Materials and Methods

In this double-blind clinical trial, the study population included all present candidates for eye surgery in Feiz hospital from March 21, 2019, to March 19, 2020. Of this population, according to the literature suggesting systolic blood pressure (SBP) standard deviations (SDs) of 12.9 and 19.2 and 11.2 as the minimum difference of the average changes of SBP in in two groups of the study,[11] we assigned patients (a total of 128 cases) to groups of 32 patients as samples (confidence interval: 95%, power of the test: 80%). To select these samples, we used consecutive sampling for patients who have indications for cataract surgery with general anesthesia and placement of the LMA. Inclusion criteria were the age >18, American Society of Anesthesiologist (ASA) Classes I or II and being consent to attend the study.

The patients with underlying or systemic diseases including uncontrolled kidney or heart failures were not included. In addition, whenever the anesthesiologist recognized that anesthetic method should change or complications occurred during the surgery, the case was excluded or replaced with another.

The proposal was approved by ethic committee of Isfahan University of Medical Sciences (ethical code: IR.MUI.MED.REC.1398.448) and the clinical trial code was obtained (IRCT20171030037093N27). In addition, after obtaining a written informed consent from all eligible patients, we recorded demographic information such as age, sex, ASA class, weight, height, and body mass index. The permuted block randomization was applied to assign patients to four groups [Figure 1].

We administered to first group (Group T + M) a combination of midazolam (0.04 mg/kg) and thiopental (2.5 mg/kg) and to second group (Group P) propofol (2.5 mg/kg) alone and to third group (Group ET + P) a combination of etomidate (0.1 mg/kg) and propofol (1 mg/kg) and to fourth group (Group T) thiopental (5 mg/kg) alone.[11,18]

In order to meet blindness, the drugs were prepared by an anesthesiologist before the intervention. Two syringes were prepared for each group. As only one drug was used for two of the groups, distilled water was embedded in one of the syringes. Considering the difference in the color of the drugs, the syringes were enclosed with covers so that the difference between the drugs was not clear. In terms of the amount of the drug, all drugs reached the same volume using distilled water. These syringes were coded and placed in the operating room. Without knowing the type of drugs, the researchers daily used two syringes packed as one group for each patient.

The hemodynamic parameters of patients including SBP and diastolic blood pressure (DBP), pulse rate (PR), peripheral oxygen saturation (SpO_2), and mean arterial pressure (MAP) were examined and recorded before and immediately after anesthesia and after 1, 3 and 5 min from LMA placement. Also, we recorded surgery and anesthesia durations for each group.

Finally, the data were analyzed with SPSS software (version 23; SPSS Inc., Chicago, Ill., USA). The data were expressed as mean ± SD and frequency (%). As Kolmogorov–Smirnov test suggests the normality of data distribution, we applied the one-way analysis of

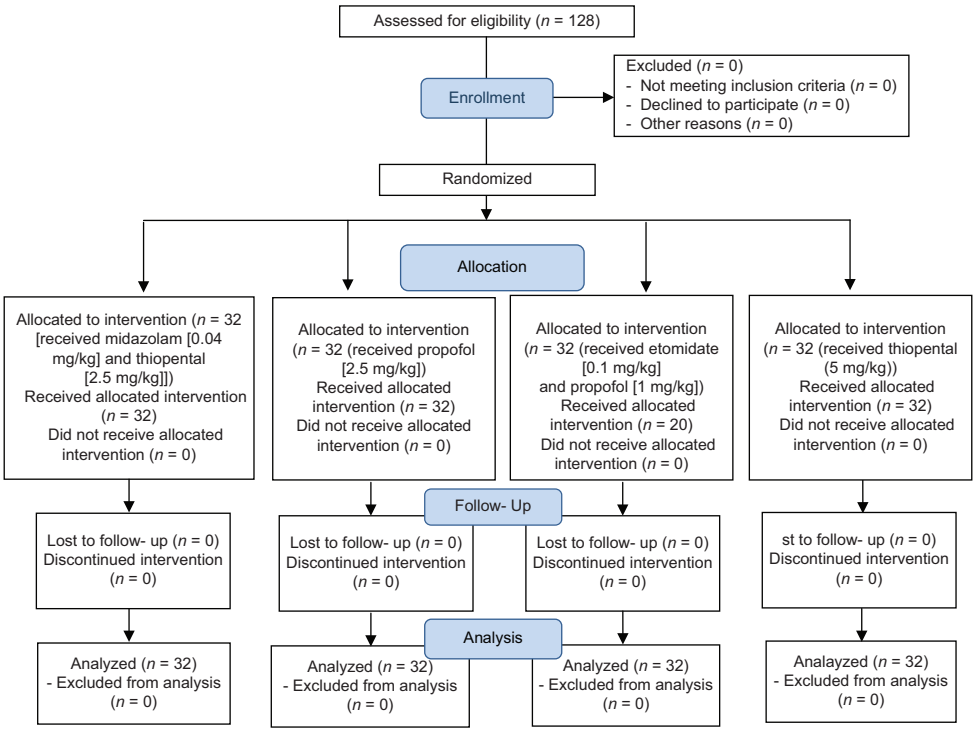

Figure 1: Consort flowchart of patients

variance (ANOVA) to compare quantitative variables in four groups and the repeated measures ANOVA to compare means across variables over the time in each group. In addition, we used Chi-square test to compare data distributions of discrete data in four groups. In all analysis, we considered a significant level of <0.05.

Results

This study included 14 males (43.8%) and 18 females (56.3%) with the mean age of 38.24 ± 10.27 years in Group T + M and 24 males (75%) and 8 females (25%) with the mean age of 37.28 ± 8.99 years in Group T and 20 males (62.5%) and 12 females (37.5%) with the mean age of 35.30 ± 10.90 years in Group ET + P and 17 males (53.1%) and 15 females (46.9%) with the mean age of 36.62 ± 9.74 years in Group P ($P > 0.05$) [Table 1].

Moreover, SBP, DBP and MAP of patients before and after anesthetic drug administration indicate no significant difference between 1 and 4 min after LMA among four groups ($P > 0.05$). However, SBP in 5th min after LMA in Group P was significantly lower than those of other groups (Group P: mmHg 113.81 ± 20.18 vs. Group T + M: 126.69 ± 19.28, Group T: 128.16 ± 23.19, Group ET + P: 121.47 ± 21.21 mmHg; $P = 0.016$). Also, the Groups T and T + M were not significantly different in terms of SBP and DBP in 5th min after LMA ($P > 0.05$). However, MAP in the Group T + M was significantly higher than the Group T (95.92 ± 13.83 vs. 91.24 ± 15.26 mmHg; $P < 0.05$). Over the time and during 5 min after LMA placement, stabilities of SBP, DBP and MAP in the Groups T and T + M were more than two other groups ($P < 0.05$) and the most instable group was the group which received propofol alone [Table 2 and Figure 2].

On the other hand, PR of patients before and after drug injection indicates no significant difference between 1 and 3 min after LMA in four groups ($P > 0.05$). However, PR level in Group P in 5th min after LMA was lower than Groups T and T + M (mean PR, Group P: 69.34 ± 13.47 vs. Group T: 73.25 ± 12.22 bpm and Group T + M: 76.78 ± 7.84 bpm; $P < 0.05$) but it was not significantly different from Group ET + P (mean PR, Group P: 69.34 ± 13.47 vs. Group ET + P: 70.72 ± 10.79 bpm; $P > 0.05$). Over the time and during 5 min after LMA placement, T + M and then T groups were with the most stable PR and just in Group P changes were significant ($P < 0.05$). SPO_2 of patents in Group P in 1 min after LMA was significantly lower than others ($P = 0.006$). Finally of patients in none of the noted times was significantly different among four groups of the study ($P > 0.05$) [Table 3 and Figure 3].

Discussion

In the current study, evaluating the stability of hemodynamic factors such as SBP and DBP indicated that there was a significant difference between the four groups only 5 min after LMA insertion. Propofol (P) groups had the lowest blood pressure levels versus thiopental (T) groups which had the highest blood pressure levels. In addition, the reduction of these two factors in Group P was significantly higher than other groups. Adding ET to P has reduced the reduction of SBP and DBP, but still has no significant

Table 1: Basic and clinical characteristics of patients in four study groups

Variables	Group T + M	Group T	Group ET + P	Group P	*P*
Sex, *n* (%)					
Male	14 (43.8)	24 (75.0)	20 (62.5)	17 (53.1)	0.070
Female	18 (56.3)	8 (25.0)	12 (37.5)	15 (46.9)	
Age (years)	38.24±10.27	37.28±8.99	35.30±10.90	36.62±9.74	0.692
ASA, *n* (%)					
I	14 (46.7)	11 (40.7)	10 (31.3)	15 (50.0)	0.459
II	16 (53.3)	16 (59.3)	22 (68.8)	15 (50.0)	
Weight (kg)	66.61±10.64	73.28±14.45	68.06±11.36	70.48±11.81	0.146
Height (cm)	164.39±8.05	169.29±8.54	166.44±9.95	168.19±9.07	0.154
BMI (kg/m^2)	24.69±3.62	25.33±3.96	24.62±3.95	24.86±3.45	0.881
Surgery duration (min)	70.00±27.17	71.43±23.79	78.21±23.92	70.96±26.61	0.844
Time of sedation (min)	76.84±23.82	82.75±28.67	75.00±26.31	80.58±21.81	0.841

ASA: American Society of Anesthesiologist, BMI: Body mass index

Table 2: Determination and comparison of systolic blood pressure, diastolic blood pressure and mean arterial pressure of patients in four study group

Variables	Group T + M	Group T	Group ET + P	Group P	P_1
SBP (mmHg)					
Baseline	130.69±20.40	135.03±21.50	131.97±22.27	133.13±14.79	0.859
T_0	128.06±10.92	133.11±18.06	130.97±20.12	125.03±13.97	0.358
T_1	125.75±24.23	128.19±22.49	119.19±25.56	115.56±27.31	0.155
T_3	127.09±18.84	127.19±20.22	123.69±20.26	118.22±25.02	0.086
T_5	128.16±23.19	126.69±19.28	121.47±21.21	113.81±20.18	0.016
Change	−2.53	−8.34	−10.50	−19.31	0.012
P_2	0.679	0.102	0.046	0.003	
DBP (mmHg)					
Baseline	85.25±13.34	86.22±12.27	86.59±11.78	87.25±10.61	0.934
T_0	84.20±12.08	85.83±13.02	84.91±9.92	83.15±10.02	0.826
T_1	80.25±15.25	82.63±14.30	75.41±17.20	74.03±19.28	0.064
T_3	82.91±14.60	83.59±17.46	75.13±14.57	77.50±15.89	0.072
T_5	81.31±14.31	80.41±11.99	70.00±13.61	68.06±14.79	<0.001
Change	−3.93	−5.81	−16.59	−19.18	<0.001
P_2	0.262	0.154	<0.001	<0.001	
MAP					
Baseline	102.49±14.45	100.39±14.43	101.72±14.19	102.54±10.68	0.913
T_0	97.81±16.45	95.42±17.49	90.00±19.21	87.87±21.50	0.126
T_1	98.12±16.97	97.63±14.01	91.31±12.19	91.07±10.99	0.060
T_3	95.83±13.91^a	96.93±16.63^a	87.16±15.41^b	83.31±15.27^b	0.001
T_5	95.92±13.83^b	91.24±15.26^a	82.88±13.73^b	84.95±17.05a^b	0.032
Change	−9.57	−11.15	−18.84	−21.59	0.022
P_2	0.069	0.058	<0.001	<0.001	

Baseline: Before injection of anesthetic drugs, T0: Immediately after injection of anesthetic drugs, T1: One minute after insertion of LMA, T3: Three minute after LMA, T5: Five minutes after LMA The same letters indicate no significant difference while different letters show significant difference in comparison within two groups. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, LMA: Laryngeal mask airway

1: Significance level obtained from One-way ANOVA test in comparing the mean of the variable between the four groups

2: Significance level obtained from Repeated Measures ANOVA test in comparison of the mean of the variable over time in each of the four groups

difference from Group P. In addition, the decrease in SBP and DBP in the Group T + M was less than the T group. In fact, the Group T + M had the most stable blood pressure changes compared to the Groups P and ET + P, but did not have a significant difference from the Group T.

According to the current study, Hosseinzadeh *et al*. showed that the MAP in the ET and Groups P + ET was more stable than in the Group P, while after reducing the dose of propofol and adding etomidate as an adjunct, the difference between the groups was not significant between Group ET

Table 3: Determination and comparison of pulse rate and peripheral oxygen saturation in four study groups

Variables	Group T + M	Group T	Group ET + P	Group P	P_1
PR (bpm)					
Baseline	77.00±10.78	77.47±13.17	75.31±14.11	80.59±14.05	0.426
T_0	76.10±10.23	77.03±12.36	74.90±13.64	78.15±13.71	0.565
T_1	75.78±11.41	75.50±11.69	74.94±14.65	73.19±10.25	0.868
T_3	76.56±11.50	75.75±12.31	74.28±12.54	73.69±10.31	0.668
T_5	76.78±7.84	73.25±12.22	70.72±10.79	69.34±13.47	0.015
Change	−0.22	−4.22	−6.59	−11.25	0.045
P_2	0.914	0.444	0.194	0.006	
SpO_2					
Baseline	97.44±2.23	97.38±1.69	97.50±1.24	96.41±2.28	0.073
T_0	97.85±1.98	97.63±1.01	97.71±1.14	97.04±1.88	0.633
T_1	98.78±1.04	98.63±1.04	98.69±0.82	97.94±1.11	0.006
T_3	98.78±1.07	98.53±1.19	98.53±1.04	98.13±1.10	0.113
T_5	98.22±1.02	98.47±1.37	98.53±1.02	98.19±0.99	0.347
Change	0.78	1.09	1.03	1.78	0.334
P_2	0.086	<0.001	<0.001	<0.001	

Baseline: Before injection of anesthetic drugs, T0: Immediately after injection of anesthetic drugs, T1: One min after insertion of LMA; T3: Three min after LMA; T5: Five min after LMA The same letters indicate no significant difference while different letters show significant difference in comparison within two groups. PR: Pulse rate, SpO_2: Peripheral oxygen saturation, LMA: Laryngeal mask airway
1: Significance level obtained from One-way ANOVA test in comparing the mean of the variable between the four groups
2: Significance level obtained from Repeated Measures ANOVA test in comparison of the mean of the variable over time in each of the four groups

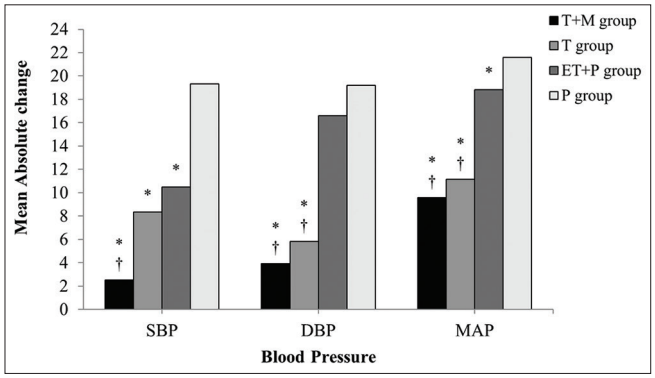

Figure 2: Determination and comparison of mean absolute changes of systolic blood pressure, diastolic blood pressure and mean arterial pressure in four study groups. *The significance level of <0.05 in comparison with Group P, †The significance level of <0.05 in comparison with Group ET + P

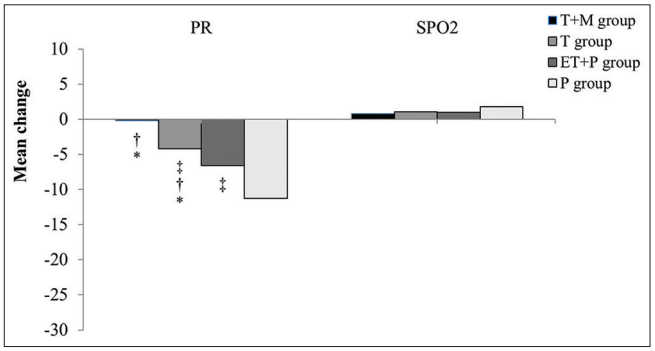

Figure 3: Determination and comparison of mean pulse rate and oxygen saturation in four groups of the study. *The significance level of < 0.05 in comparison with Group P, †The significance level of < 0.05 in comparison with Group ET + P, ‡The significance level of < 0.05 in comparison with Group T + M

and Group P + ET in increasing hemodynamic stability. They also stated that the highest blood pressure drop (after LMA insertion) was in the Group P.[11]

Saricaoglu *et al*. also showed that the hemodynamic variables in Group P + ET had the highest stability compared to the Groups P and ET and MAP in Group P had the highest decrease compared to other groups.[21]

Another study found that changes in intraocular pressure in Group P were significantly higher than in Group T 2 min after anesthesia. In addition, a decrease in SBP after anesthesia and an increase after LMA was seen in all three groups (recipients of T, ET, and P). SBP changes were not significant in the ET and Groups T after LMA insertion compared to baseline. In fact, the stability of SBP in the Groups ET and T was higher than Group P.[5]

Moosavi *et al*. also suggested that although the mean changes of SBP and DBP before and 5 min after intubation in Group P (12% and 15%, respectively) were higher than Group ET (5% and 6%, respectively), but statistically this difference was not significant.[22]

On the other hand, midazolam has little effect on blood pressure and heart rate, and according to the findings of this study and other studies, blood pressure drop of midazolam is lower than that of thiopental[23,24] and therefore midazolam can even be used in patients with severe aortic stenosis to induce anesthesia.[8,25]

On the other hand, PR changes between the four groups were significant within 5 min after LMA insertion. As

in Group P, the highest PR decrease was observed. In addition, the addition of etomidate to the propofol (ET + P) has significantly increased PR stability compared to the Group P. The addition of midazolam to thiopental (T + M) has minimized PR changes compared to the Group T. Therefore, it can be said that T + M prescribing can be the best drug combination to reduce patients' PR changes, and in cases where thiopental (T) administration is not recommended for the patient, prescribing ET + P drug combination will be associated with less hemodynamic changes. In addition, the differences between SPO_2 did not differ significantly between the four study groups.

In line with the present study, many previous studies have shown that heart rate in Group P had been significantly reduced compared to Group ET, but there were no difference between P and P + ET groups.[11,12,26] Another study indicated that the changes in heart rate and SPO_2 in Group P were higher than those in Group ET.[22] Therefore, propofol may be recommended for patients who require appropriate postoperative cooperation (such as patients with chronic obstructive pulmonary disease) and etomidate may be recommended in patients with hemodynamic problems.

Shetabi *et al*. in comparing the hemodynamic response of thiopental sodium-midazolam combination showed that use of thiopental sodium-midazolam combination was effective and safe and attenuated the stress response to airway management with resultant minimal changes in the heart rate and blood pressure.[27]

On the other hand, in the induction of anesthesia with midazolam (M), patients are anesthetized later, so previous studies have shown that post-LMA heart rate changes in Group M were higher than that in Group T, which is known to be delayed at the onset of anesthesia. This is problematic in emergencies that require rapid induction of anesthesia and LMA.[28,29] Other studies have shown that thiopental has a negative inotropic effect on the heart and arteries, but Midazolam does not have this depression.[29,30]

Other studies have also shown better stability of patients' hemodynamic status (blood pressure and heart rate) in Group M compared to Group T.[30,31] In contrast, thiopental has been shown to be the best choice for inducing anesthesia in patients undergoing neurosurgery due to its marked effects on lowering intracranial pressure and cerebral blood flow.[32,33] And midazolam can be a good alternative to thiopental in asthmatic patients who are not hemodynamically stable or in patients with porphyria who have contraindications for thiopental.[34]

Due to the properties of each of the four drugs and their advantages and disadvantages, co-induction can be used in patients with specific and critical conditions. For example, using the proper dose of thiopental, it quickly induced anesthesia[29] and its combination with midazolam (T + M) eliminated the adverse effects of thiopental due to hemodynamic changes. Or combining etomidate (ET) with propofol (P) can prevent low blood pressure and heart rate. In our study, attention was paid to the combination of T + M as well as ET + P to control these changes as much as possible, and as the results of our study, patients in these combination groups were less likely to have hemodynamic changes. Each of these drugs (T and P groups) has been used individually.

It should be noted that in this study, specific doses were used for the administration of midazolam, thiopental, etomidate and propofol, and the administration of additional doses of drugs was not considered. Although many other studies have evaluated the effects of these drugs in combination with other drugs such as ketamine, remy fentanyl, atracurium,[35-38] this study is the only study to combine the four types of drugs individually and in combination with each other to neutralize other disadvantages and this can be a strength of the current study. And to confirm the results of this study, it is recommended that more clinical trials with these drug combinations should be performed in patients with various diseases and undergoimg other types of surgery.

Conclusion

According to the results of the current study, a combination of midazolam-thiopental (T + M) may serve as an effective and safe induction agent for reducing hemodynamic responses to laryngoscopy and intubation, with greater hemodynamic stability compared to thiopental alone, propofol alone and combination of etomidate in patients undergoing surgery in general anesthesia.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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