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Comparative Evaluation of Effect of Propofol, Etomidate and a Combination of Propofol and Etomidate on the Hemodynamic Response to Induction and Endotracheal Intubation: A Prospective Randomized Double Blinded Study

Propofol, Etomidat ve Propofol ve Etomidat Kombinasyonunun İndüksiyon ve Endotrakeal Entübasyona Hemodinamik Yanıt Üzerindeki Etkisinin Karşılaştırmalı Değerlendirmesi: Prospektif, Randomize, Çift Kör Bir Çalışma

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ABSTRACT

Objective: Earlier studies have shown favorable hemodynamics with etomidate compared to propofol. Our study aimed to compare the hemodynamic characteristics of intravenous induction with precalculated doses of propofol, etomidate, and a combination of propofol-etomidate in adult surgical patients.

Methods: One hundred twenty six patients aged 18 to 50 years of either sex and ASA physical status I scheduled for various surgeries under general anesthesia were recruited. Patients were randomized into three groups. Group P-induced with pre-calculated propofol (2 mg kg^{-1}) intravenous, Group E with etomidate (0.3 mg kg^{-1}) intravenous, and Group PE with propofol (1 mg kg^{-1}) plus Etomidate (0.2 mg kg^{-1}) intravenous. Heart rate, systolic, diastolic, and mean arterial blood pressure at baseline, 2, and 3 minutes after induction and then at 1, 3, 5, and 10 minutes after endotracheal intubation were noted.

Results: The percentage change in hemodynamic parameters was significant from the baseline value in the propofol group compared to the etomidate and combination group at all the time intervals. The change in hemodynamic parameters from the baseline value was comparable at 2 and 3 minutes post-induction between etomidate and combination group. At other time intervals, the etomidate group tends to have an increase from the baseline while the combination has less significant change from the baseline value compared to etomidate group.

Conclusion: The percentage change in the hemodynamic parameters from the baseline value was less in the combination group compared to the etomidate or propofol group.

Keywords: Etomidate, propofol, hemodynamics, intubation

ÖZ

Amaç: Daha önceki çalışmalar, propofole kıyasla etomidat ile olumlu hemodinami göstermiştir. Çalışmamızda cerrahi geçiren erişkin hastalarda önceden hesaplanmış propofol, etomidat ve propofol-etomidat kombinasyonu ile intravenöz indüksiyonun hemodinamik özelliklerini karşılaştırmayı amaçladık.

Yöntem: Genel anestezi altında çeşitli ameliyatlar için planlanmış, yaşları 18 ile 50 arasında değişen, her iki cinsiyetten ve ASA fiziksel durumu I olan 126 hasta çalışmaya alındı. Hastalar randomize olarak üç gruba ayrıldı. Grup P- önceden hesaplanmış intravenöz propofol (2 mg kg^{-1}), Grup E intravenöz etomidat (0.3 mg kg^{-1}) ve Grup PE intravenöz propofol (1 mg kg^{-1}) artı etomidat (0.2 mg kg^{-1}) ile indüklendi. Kalp hızı, sistolik, diyastolik ve ortalama arteriyel kan basıncı, başlangıçta, indüksiyondan 2 ve 3 dakika sonra ve ardından endotrakeal entübasyondan 1, 3, 5 ve 10 dakika sonra kaydedildi.

Bulgular: Hemodinamik parametrelerdeki yüzde değişim, tüm zaman aralıklarında etomidat ve kombinasyon grubu ile karşılaştırıldığında propofol grubunda başlangıç değerinden anlamlıydı. Başlangıç değerine göre hemodinamik parametrelerdeki değişiklik, etomidat ve kombinasyon grubu arasında indüksiyondan 2 ve 3 dakika sonra farklıydı. Diğer zaman aralıklarında, etomidat grubu başlangıca göre bir artış eğilimi gösterirken, kombinasyon grubu etomidat grubuyla karşılaştırıldığında başlangıç değerinden daha az anlamlı bir değişime sahipti.

Sonuç: Başlangıç değerine göre hemodinamik parametrelerdeki yüzde değişim kombinasyon grubunda etomidat veya propofol grubuna göre daha azdı.

Anahtar sözcükler: Etomidat, propofol, hemodinamik parametreler, entübasyon

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INTRODUCTION

The advances in surgical intervention have been possible with the enhanced safety achieved in the conduct of general anesthesia. In the conductance of general anesthesia, the induction period is a critical period at which enormous fluctuations in hemodynamics occur (1). The available intravenous induction agents like propofol, etomidate, and thiopentone are all known to cause hemodynamic instability and hence various strategies to avoid these hemodynamic perturbations during intravenous induction of general anesthesia were adopted in clinical practice (2, 3). Tracheal intubation is another intervention that happens soon after induction of general anesthesia which also contributes to the hemodynamic alterations (4). The dosage and the rate of administration of these induction agents have been shown to modify the degree of hemodynamic changes occurring during induction of general anesthesia (5). Etomidate has been claimed by many anaesthesiologists to have stable hemodynamics during induction of general anesthesia except for the unwanted incidence of myoclonus, suppression of the hypothalamic-pituitary axis, and pain on injection. Few of the earlier studies have studied the effect of the combination of etomidate and propofol (6). This study is based on the hypothesis that the combination of etomidate and propofol will have less effect on hemodynamic changes during induction and endotracheal intubation during general anesthesia. This study aimed to compare the hemodynamic characteristics of intravenous induction with a precalculated dose of propofol, etomidate, and a combination of propofol and etomidate in terms of systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) as well as heart rate (HR) following induction and endotracheal intubation in patients coming for various surgeries under general anesthesia with endotracheal intubation.

MATERIAL and METHODS

After getting Institutional Ethics Committee approval (IE20/OCT/159/43 dated 04/01/2021) and patient consent, this study was conducted at a tertiary care center. This study was designed as a prospective randomized study. The sample size was calculated based on the previous article with the heart rate as the primary outcome and arrived to be 42 patients in each group (6). One hundred twenty six patients aged 18-50 years of either sex belonging to ASA physical status I scheduled for various surgeries under general anesthesia were selected. Exclusion criteria being: patient refusal, emergency surgery requiring rapid sequence induction, allergy to propofol/etomidat, and clinical predictors of an anticipated difficult airway. Randomization was done by computer-generated block randomization and concealed by sealed envelopes, and the patients were divided into 3 groups. Group P received a pre-calculated dose of propofol 2 mg kg^{-1} intravenous for induction while Group E received etomidate 0.3 mg kg^{-1} intravenous and Group PE received a combination containing pre-calculated dose of propofol 1 mg kg^{-1} and etomidate 0.2 mg kg^{-1} intravenously for induction of general anesthesia. Patients who fit into the inclusion criteria were enrolled in the study and general anesthesia as well as the various induction agents were explained to them along with their advantages and disadvantages following which their consent was obtained. A basic preoperative assessment was done on the previous day and baseline investigations were noted and they were kept nil per oral for 8 hours.

The patients were shifted into the operating room and all the standard ASA monitors were attached namely electrocardiography, non-invasive blood pressure (NIBP), and pulse-oximetry. Baseline hemodynamic values were recorded. Baseline (preoperative) HR, SBP, DBP, and MAP were recorded. Patients were pre-oxygenated for 3 minutes with 100% O_2, following which induction was started with intravenous injection of fentanyl 2 µg kg^{-1}. After 5 minutes of fentanyl administration, they received the intravenous induction agent based on the group into which they were allotted.

Dosages were pre-calculated and loaded in two masked 10 mL syringes in Group P and E. In Group PE, propofol was loaded in one masked syringe and etomidate in the other masked syringe. Syringes were masked in such a way that the entire barrel of the syringe was covered with black paper with only the plunger uncovered.

The doses were pre-calculated based on the patient weight and loaded by an anaesthesiologist that was not present inside the operation room, the syringes were masked and shifted along with the patient. The drugs were administered by an anaesthesiologist who was blinded to the study drug. The drug was injected in one syringe after the other over thirty seconds.

After the loss of response to verbal commands vecuronium 0.1 mg kg^{-1} intravenous was given. After three minutes of vecuronium administration, laryngoscopy and endotracheal intubation were performed by an experienced anaesthesiologist in all patients. An endotracheal tube size of 7.5 was cuffed in female patients and 8.5 size cuffed was used in male patients. Maintenance of general anesthesia was done with sevoflurane (2%) and an air-O_2 mixture (3 L min^{-1}) was started immediately after the loss of response to verbal commands. Care was taken that no external stimulus in any form was given to the patient till 10 minutes after intubation from the induction of general anesthesia. Then the patient was handed over to the surgeon. After the study period the inhaled sevoflurane was adjusted based on the necessity at the discretion of the attending anesthesiologist.

Hemodynamic parameters (HR, SBP, DBP, MAP) were recorded at pre-induction Baseline (T0), 2 minutes after induction (T1), 3 minutes after induction (T2), at 1 minute after intubation (T3), 3 minute after intubation (T4), 5 minute after intubation (T5), and 10 minutes after endotracheal intubation (T6). In case of hypotension more than 20% of baseline, rescue dose of vasopressor ephedrine 6 mg intravenous was given. If systolic blood pressure increases more than 160 $mmHg^{-1}$ it was treated with esmolol 0.5 mg kg^{-1}. In case of a fall in heart rate less than 60 beats per minute with blood pressure less than 90/60 mmHg they were treated with atropine 1 mg intravenous. If the heart rate increased above 100 beats per minute esmolol 0.5 mg kg^{-1} was given. The number of such degrees of hemodynamic perturbations was recorded. At the end of the procedure, neuromuscular blockade was antagonized by neostigmine 0.05 mg kg^{-1} intravenous and glycopyrrolate 0.01 mg kg^{-1} intravenously and were extubated following the return of adequate reversal of neuromuscular blocking agents at the end of the procedure.

The secondary outcomes noted are the presence of pain on injection as well as the incidence of myoclonus. The presence of grimace, tearing, or outright complaints of pain during the injection of the drug was considered as pain on injection. Myoclonus was defined as the myoclonic movement of the face, shoulders, or any one or more body segments. The expected dropouts from the study were the need for more than two attempts at endotracheal intubation by the experienced anaesthesiologist and extreme hemodynamic perturbations during induction which needed pharmacological intervention as stated above.

Statistical Power Analysis

It was calculated according to the previous study (6). To find the significant difference in the change in heart rate, with an effect size of 5.9 at a standard deviation of 6.8, and an effect size of 6.1 at a standard deviation of 7.4, 36 cases were required in each group with a power of 80% at a 5% alpha error. (α=0.05, β=0.80). With an expected drop rate of 15% a total size of 42 cases in each group was arrived. The collected data were analyzed with IBM SPSS Statistics for Windows, Version 23.0. (Armonk, NY: IBM Corp), as well as JASP statistics for macOS (Amsterdam, The Netherlands). To describe the data descriptive statistics frequency analysis, and percentage analysis was used for categorical variables and the mean & SD were used for continuous variables. To find the significant difference in the multivariate analysis the ANOVA test was used. To find the significance in categorical data Chi-Square test was used. In all the above statistical tools the probability value of .05 is considered a significant level.

RESULTS

All the recruited participants completed the study protocol as shown in the consort diagram (Figure 1). Table I shows the distribution of the demographic profiles among the three groups. It shows the comparable distribution of age, sex, and body mass index among the three groups. Table II shows the comparison of percentage change in SBP at different time points from the baseline between the three groups. On comparing groups B and C, it was found that the percentage change in SBP was not statistically significant between Group E and Group PE in the second and third-minute post-induction as shown in the Figure 2. At other time intervals, there was a statistically significant difference in the percentage change between Group E and Group PE. The etomidate group has shown an increasing trend post-intubation while the combination showed an increasing trend but fewer changes from the baseline compared to the etomidate group in the systolic blood pressure distribution. The change from the baseline in SBP was statistically significant at all the time intervals in the propofol Group compared to the etomidate or the combination group. Similar findings were seen in terms of the diastolic blood pressure between the various Group comparisons as shown in the Figure 2.

Table III shows the comparison of percentage change in MAP and HR at different time intervals from the baseline between the three groups. On comparing groups B and C, it was found that the percentage change in MAP and HR was not statistically significant between Group E and Group PE in the second and third-minute post-induction. At other time intervals, there was a statistically significant difference in the percentage change between Group E and Group PE. The Group E has

Table I: Comparison of Demographic Profile Among the Three Groups

Variable	Group P n=42	Group E n=42	Group PE n=42	p
Age (years)	32.3 ± 9.5	29.5 ± 9.5	27.7 ± 10.3	0.093
Body mass index (kg m^{-2})	24.1 ± 2.3	24.0 ± 2.4	23.8 ± 2.1	0.781
Sex distribution	Male: 24 (57.1%) Female: 18 (42.9%)	Male: 22 (52.4%) Female: 20 (47.6%)	Male: 20 (47.6%) Female: 22 (52.4%)	0.683

Age and body mass index were expressed as mean±SD, sex distribution as frequency %. **Group P:** Propofol, **Group E:** Etomidate, **Group PE:** Combination.

Table II: Comparison of Percentage Change in Systolic and Diastolic Blood Pressure at Various Time Points from the Baseline

Variable	Group P (%) n=42	Group E (%) n=42	Group PE (%) n=42	p Group P vs. E	p Group E vs. PE	p Group P vs. PE
Change in SBP from baseline at 2 min	-9.2 ± 9.1	-2.0 ± 3.0	-2.6 ± 2.0	<0.001	0.295	<0.001
Change in SBP from baseline at 3 min	-17.5 ± 6.2	-3.3 ± 3.6	-3.9 ± 2.3	<0.001	0.392	<0.001
Change in SBP from baseline at 1 min PI	-12.0 ± 7.53	10.5 ± 8.3	0.2 ± 3.6	<0.001	<0.001	<0.001
Change in SBP from baseline at 3 min PI	-12.6 ± 7.1	8.6 ± 9.4	-1.2 ± 4.5	<0.001	<0.001	<0.001
Change in SBP from baseline at 5 min PI	-13.5 ± 5.9	5.7 ± 9.6	-2.0 ± 4.2	<0.001	<0.001	<0.001
Change in SBP from baseline at 10 min PI	-13.9 ± 5.6	3.6 ± 8.6	-2.5 ± 4.8	<0.001	<0.001	<0.001
Change in DBP from baseline at 2 min	-10 ± 11.6	-1.9 ± 4.6	-1.7 ± 2.8	<0.001	0.862	<0.001
Change in DBP from baseline at 3 min	-13.0 ± 12.9	-2.3 ± 5.4	-1.6 ± 4.3	<0.001	0.517	<0.001
Change in DBP from baseline at 1 min PI	-6 ± 10.0	15.7 ± 15.8	2.6 ± 5.6	<0.001	<0.001	<0.001
Change in DBP from baseline at 3 min PI	-7.5 ± 9.5	13.5 ± 20.8	2.0 ± 6.0	<0.001	<0.001	<0.001
Change in DBP from baseline at 5 min PI	-7.8 ± 9.6	11.6 ± 18.3	1.1 ± 5.1	<0.001	<0.001	<0.001
Change in DBP from baseline at 10 min PI	-8.4 ± 9.5	8.3 ± 13.4	0.0 ± 5.6	<0.001	<0.001	<0.001

Group P: Propofol, **Group E :** Etomidate, **Group PE:** Combination, **PI:** Post induction, **SBP:** Systolic blood pressure, **DBP:** Diastolic blood pressure, **min:** Minutes. Hemodynamic parameters presented as mean ±SD.

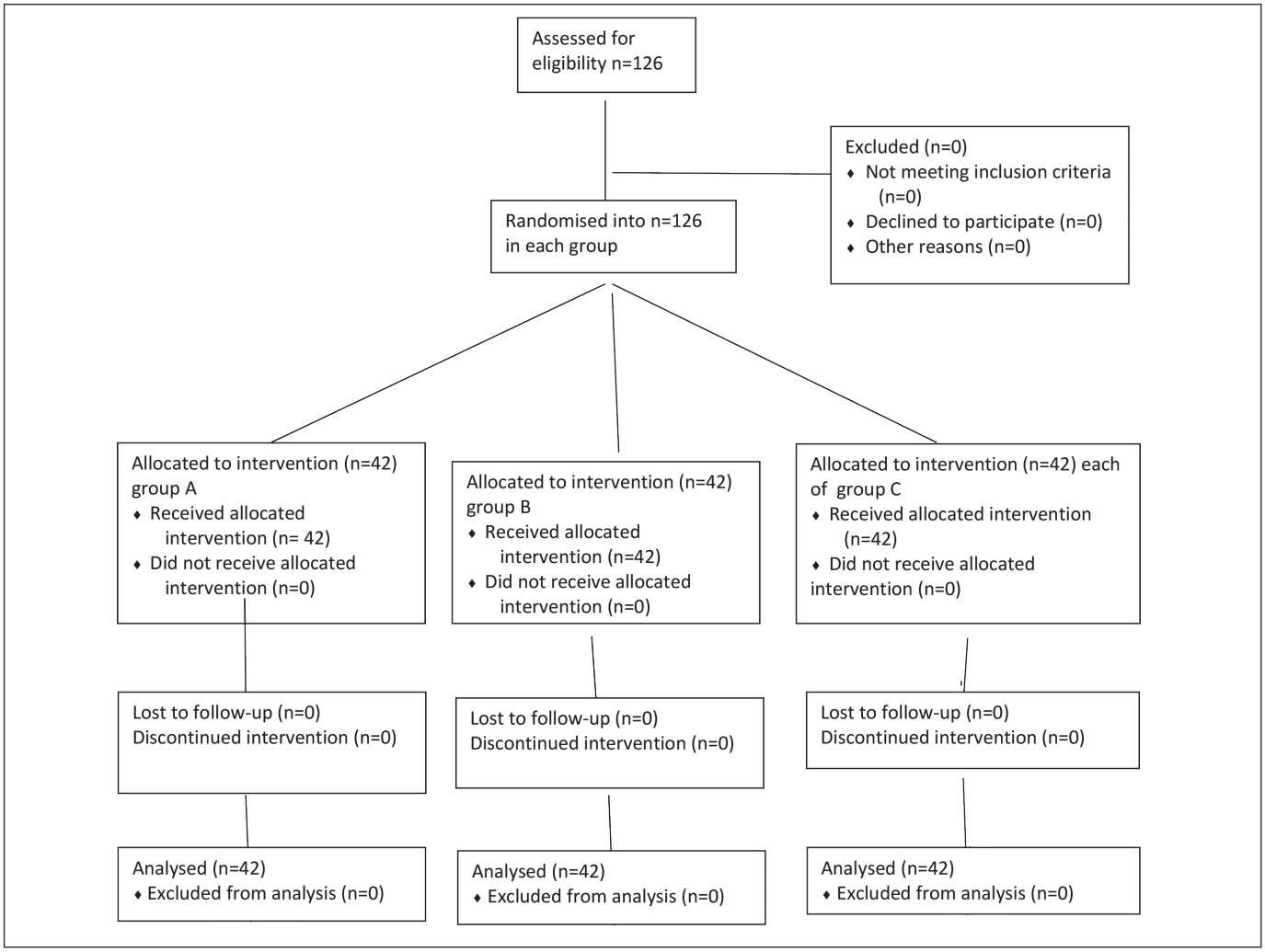

Figure 1: Consort diagram.

shown an increasing trend post-intubation while the combination group showed an increasing trend but fewer changes from the baseline compared to the etomidate group in the systolic blood pressure distribution. The change from the baseline in MAP and HR was statistically significant at all the time intervals in Group P compared to Group E or Group PE.

Table III: Comparison of Percentage Change in Mean Arterial Pressure and Heart Rate at Various Time Points from the Baseline

Variable	Group P (%) n=42	Group E (%) n=42	Group PE (%) n=42	p Group P vs. E	p Group E vs. PE	p Group E vs. PE
Change in MAP from baseline at 2 min	-10.1 ± 9.2	-1.9 ± 3.3	-1.7 ± 2.5	<0.001	0.719	<0.001
Change in MAP from baseline at 3 min	-15.5 ± 9.3	-2.8 ± 3.8	-2.1 ± 3.0	<0.001	0.429	<0.001
Change in MAP from baseline at 1 min PI	-8.6 ± 7.9	13.2 ± 11.2	2.0 ± 4.5	<0.001	<0.001	<0.001
Change in MAP from baseline at 3 min PI	-9.4 ± 7.5	11.1 ± 13.5	0.1 ± 4.3	<0.001	<0.001	<0.001
Change in MAP from baseline at 5 min PI	-10.0 ± 6.9	8.7 ± 12.9	0.1 ± 4.3	<0.001	<0.001	<0.001
Change in MAP from baseline at 10 min PI	-10.4 ± 6.6	6.1 ± 10.1	-0.6 ± 4.9	<0.001	<0.001	<0.001
Change in HR from baseline at 2 min	-7.3 ± 10.1	-2.1 ± 5.7	-2.4 ± 3.6	0.004	0.724	0.004
Change in HR from baseline at 3 min	-7.6 ± 12.1	-4.1 ± 7.1	-3.1 ± 4.2	0.009	0.447	0.026
Change in HR from baseline at 1 min PI	-1.6 ± 11.8	11.3 ± 10.5	0.6 ±4.9	<0.001	<0.001	0.253
Change in HR from baseline at 3 min PI	-3.4 ± 12.8	8.4 ± 11.4	-1.2 ± 4.8	<0.001	<0.001	0.296
Change in HR from baseline at 5 min PI	-4.1 ± 11.4	4.9 ± 11.1	-1.8 ± 5.0	<0.001	<0.001	0.250
Change in HR from baseline at 10 min PI	-5.1 ± 10.8	-2.8 ± 5.4	-2.8 ± 5.4	<0.001	0.002	0.235

Group P: Propofol, **Group E:** Etomidate, **Group PE:** Combination, **PI:** Post induction, **MAP:** Mean arterial pressure, **HR:** Heart rate. Hemodynamic parameters presented as mean±SD.

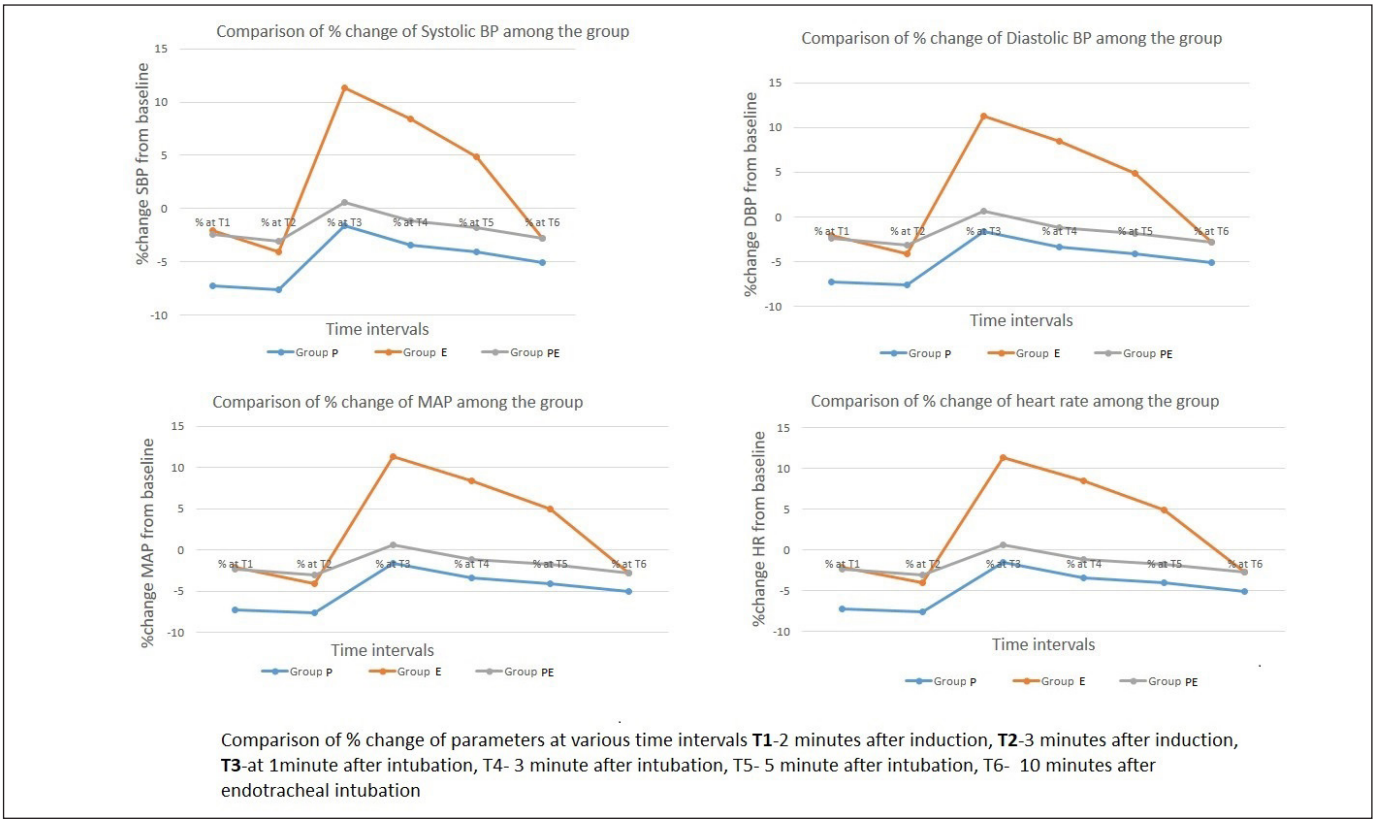

Figure 2: Comparison of hemodynamic study parameters at various time intervals between the three groups. **Group P:** Propofol, **Group E:** Etomidate, **Group PE:** Combination, **BP:** Blood pressure, **SBP:** Systolic blood pressure, **DBP:** Diastolic blood pressure, **MAP:** Mean arterial pressure, **HR:** Heart rate.

Table IV: Comparison of Pain on Injection between the Three Groups

			Groups			Total	c^2- value p-value	
			Group P n=42	Group E n=42	Group PE n=42			
Injection pain	No	Count	32	30	34	96	1.050	0.592
		%	76.2%	71.4%	81.0%	76.2%		
	Yes	Count	10	12	8	30		
		%	23.8%	28.6%	19.0%	23.8%		
	Total	Count	42	42	42	126		
		%	100.0%	100.0%	100.0%	100.0%		
Myoclonus	No	Count	42	36	40	118	7.475	0.024
		%	100.0%	85.7%	95.2%	93.7%		
	Yes	Count	0	6	2	8		
		%	0.0%	14.3%	4.8%	6.3%		
	Total	Count	42	42	42	126		
		%	100.0%	100.0%	100.0%	100.0%		

Group P: Propofol, **Group E:** Etomidate, **Group PE:** Combination. Pain on injection and myoclonus presented as frequency %.

Table IV shows the comparison of Pain on Injection between the three Groups. There was no statistically significant difference between Injection pain among the three Groups. There was a statistically significant difference in the incidence of myoclonus which was more in Group E compared to the combination and was not observed in the Group P.

DISCUSSION

Propofol is commonly used for the induction of general anesthesia. Studies have observed hypotension and bradycardia during this process (7). Similarly, the use of etomidate for induction has been shown to have a stable hemodynamic but has shown an increased incidence of hemodynamic response including hypertension and tachycardia during endotracheal intubation (8). Our study shows a comparatively stable hemodynamic profile with the usage of a combination of propofol and etomidate similar to the previous study (6). This combination of etomidate and propofol has also been shown to achieve other advantages like better Laryngeal Mask Airway (LMA) insertion and placement as well as the number of attempts required for proper placement of the LMA (9). One of the notable complications of etomidate was the incidence of myoclonus which was found to be not decreased by the combination of propofol with etomidate in our study compared to earlier studies showing a reduced incidence of myoclonus with the combination to that of etomidate alone (10).

The most prominent effect of propofol on hemodynamics is a decrease in arterial blood pressure during induction of anesthesia which is primarily because of the peripheral vasodilatation and ultimately the decrease in cardiac output (2). Independent of cardiovascular disease an induction dose of 2 to 2.5 mg kg^{-1} produces a 25% to 40% reduction of systolic blood pressure (11). The claimed hemodynamic stability seen with etomidate is caused by its lack of effect on the sympathetic nervous system and on the function of the µµbaroreceptor (11). The cardiovascular effects of propofol are dose-dependent. Hence, the addition of the cardio-stable etomidate to the propofol decreases the total dosage required for the induction of general anesthesia and also achieves stable hemodynamics both during induction and the period of laryngoscopy and endotracheal intubation.

The limitations of our study include the fact that we did not use Bispectral index monitoring (BIS) to evaluate the depth of anesthesia and guide the dosage of the study drugs. Bispectral index monitoring has been shown to improve anesthetic delivery and postoperative recovery (12). The authors sincerely realize the added cost of the monitoring. It was also shown that the difference in the requirement of propofol for induction of anesthesia is not significant when using BIS monitoring compared to the clinical endpoint of loss of verbal response (13). Earlier literature shows the effect of etomidate on the hypothalamic pituitary axis, measurement of adrenocorticotropic hormone and plasma cortisol level could have been added to evaluation in this study. However, studies have shown that a single dose of etomidate does not cause significant adrenal suppression (14). This deficiency in our study finds the scope for future research in this clinical area of interest.

CONCLUSION

Hence, the percentage change in the hemodynamic parameter from the baseline value was less in the combination group compared to the etomidate or propofol group. This study concludes that the combination of propofol 1 mg kg^{-1} body weight and etomidat 0.2 mg kg^{-1} body weight produces more stable hemodynamic alterations in adult patients undergoing various procedures when compared to propofol or etomidate alone.

AUTHOR CONTRIBUTIONS

Conception or design of the work: VV, VS
Data collection: VV, VS
Data analysis and interpretation: VV, VS
Drafting the article: VV, VS
Critical revision of the article: VV, VS
The author (VV, VS) reviewed the results and approved the final version of the manuscript.

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