Archives of Anesthesiology and Critical Care (In Press); x(x): xx-xx.

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Research Article

Comparison of Hemodynamic Responses to Ketofol versus Etomidate During Anesthesia Induction in Elderly Patients

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ARTICLE INFO

Article history:
Received 13 November 2023
Revised 04 December 2023
Accepted 18 December 2023

Keywords:
Etomidate;
Hemodynamic;
Endotracheal intubation;
Ketamine;
Peripheral oxygen saturation

ABSTRACT

Background: Nausea While elderly patients are at an increased risk of perioperative morbidity and mortality; old age alone is not a contraindication for surgery. General factors that should be considered in preoperative risk assessments include age, functional status, cognition, nutritional status, and comorbidities, such as cardiac, pulmonary, renal, and endocrine disorders. Induction of anesthesia is a critical step in surgery, particularly for elderly patients and those with a high physical status. Commonly used drugs for this purpose include etomidate and propofol. Therefore, this study aimed to compare the impact of Ketofol versus etomidate alone on the hemodynamic status of patients who fall under the ASA class II or higher.

Methods: The study was a prospective randomized double-blind clinical trial, with a study population of age of ≥65 years, ASA physical status class II or higher, that were randomized into two groups. Ketofol (n=45) and, Etomidate (n=45) groups. Patients followed for clinical outcomes including their hemodynamic status during the induction period.

Results: The present study showed that, the examination of hemodynamic parameters up to 10 minute after laryngoscopy showed that none of these parameters were significantly different between the two groups, while immediately after anesthesia induction, heart rate and blood pressure were found to be significantly different. However, there was no significant difference in terms of SPO2 among the two groups in any given interval.

Conclusion: The results of the present study revealed that Ketofol resulted in better regulation and stability of blood pressure and heart rate in patients undergoing endotracheal intubation, compared to etomidate alone.

Introduction

Trauma Aging is associated with some physiological changes in vital organs, such as cardiovascular and respiratory systems, central nervous system, kidneys, liver, digestive system, and metabolic processes [1-3]. While elderly patients are at an increased risk of perioperative morbidity and mortality, old age alone is not a contraindication for surgery [4-5]. General factors that should be considered in preoperative risk assessments include age, functional status, cognition, nutritional status, and comorbidities, such as cardiac, pulmonary, renal, and endocrine disorders. However, when comparing the impact of age and comorbidities on postoperative outcomes, the latter proves to be a more accurate predictor of postoperative complications. Additionally, functional limitations can heighten the risk associated with surgery. Therefore, a preoperative evaluation of functional status, including routine daily activities and instrumental activities of daily living, can provide valuable insights [6-8].

There is no single anesthetic technique or drug that is universally preferred in geriatric surgery [9]. However,

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understanding the pharmacokinetics of anesthetic drugs and the impact of age-related changes can significantly influence the dosage determination. Considerations for the induction and administration of anesthesia in elderly patients include reducing the concentration of inhaled anesthetics, decreasing the initial dose of narcotics, making small to moderate reductions in the need for segmental doses, anticipating the prolonged effects of local anesthesia, lowering the initial dose of benzodiazepines, increasing the required dose of atropine to elicit a similar cardiac response, predicting the possibility of central anticholinergic syndrome, and increasing the required dose of isoproterenol to achieve a similar heart rate response [10].

Among intravenous anesthetics, propofol is highly fat-soluble and rapidly induces unconsciousness when administered intravenously. For elderly patients, reduction of its induction dose or slow titration is recommended. The age-related decline in the clearance of propofol can reduce the need for this drug with aging. Propofol, when used to induce anesthesia in elderly patients, can cause a significant decrease in systemic blood pressure due to its negative inotropic and vasodilatory effects. Nonetheless, these characteristics may make it more advantageous than thiopental for a quicker recovery of cognitive function [11]. Overall, propofol, as a widely used anesthetic for anesthesia induction and intubation, can cause a significant drop in blood pressure, which is one of its notable side effects [12].

Etomidate quickly induces unconsciousness and is often utilized for anesthesia induction in elderly patients with cardiovascular instability. The initial distribution volume of etomidate decreases with age, meaning that a 12-year-old patient requires less than half the dose of etomidate to achieve the same level of electroencephalogram suppression as compared to younger patients [13]. Both etomidate and propofol are short-acting intravenous drugs with similar half-lives. They offer rapid recovery post-injection and appear to be suitable for inducing anesthesia in individuals with a good physical condition [14-15]. Etomidate administration results in minor alterations in hemodynamic status, whereas the use of propofol for anesthesia induction can lead to a decrease in arterial blood pressure [16-17].

Ketamine is an anesthetic drug that acts as a depressant of the central nervous system [12,18]. Compared to other psychoactive substances, ketamine is considered less hazardous, as it does not suppress respiration or circulation, and it does not inhibit the gag reflex [18]. However, it is important to note that ketamine can induce hallucinogenic effects in humans. This drug is commonly used to induce anesthesia and relieve pain in humans. It is a schedule III substance, which has been approved for use in hospitals and clinics. Its side effects can include hallucinations, sedation, and a sense of detachment.

Due to the high prevalence of comorbidities, such as cardiovascular and pulmonary diseases, in elderly patients undergoing major surgeries, particularly those that may involve prolonged procedures or significant shifts in body fluid volumes, the use of invasive monitoring methods, such as arterial and central venous catheterization, should be considered [19]. Cardiovascular complications (e.g., cardiac dysrhythmia, myocardial ischemia, and congestive heart failure) can have significant effects on postoperative outcomes in elderly patients. Perioperative planning involves identifying elderly patients at a high risk of postoperative cardiovascular complications, optimizing preoperative medical treatments, managing known risk factors prior to surgery, implementing pharmacological interventions, and devising a postoperative care strategy [20].

Objectives

According to the physical status classification system by the American Society of Anesthesiologists (ASA), patients classified as ASA II require significant attention in terms of anesthesia monitoring, as well as preoperative and intraoperative measures. Implementation of care measures is crucial to minimize complications during and after surgery. Induction of anesthesia is a critical step in surgery, particularly for elderly patients and those with a high physical status. Commonly used drugs for this purpose include etomidate and propofol. However, there is a lack of extensive research on patients aged ≥65 years, who are classified as ASA class II or higher. Therefore, this study aimed to compare the impact of Ketofol versus etomidate alone on the hemodynamic status of patients who fall under the ASA class II or higher.

Methods

This triple-blind, controlled, randomized clinical trial was conducted at Al-Zahra Hospital in Isfahan, Iran, during 2021-2022. The target population consisted of patients classified as ASA II or higher, who were scheduled for surgery under general anesthesia in this center. The inclusion criteria were as follows: being eligible for elective surgery under general anesthesia, age of ≥65 years, ASA physical status class II or higher, and informed consent to participate in the study.

Meanwhile, candidates for emergency surgery, patients with a history of drug, alcohol, or chronic benzodiazepine use, individuals with a BMI >30 kg/m2, patients with a history of seizures, candidates for craniotomy surgery, individuals with adrenal insufficiency, and patients with blood pressure >110/220 mmHg were not included in the study. The exclusion criteria of this study were as follows: a change in anesthesia technique due to various reasons, difficult intubation, severe sensitivity to the anesthetic induction drugs used in the study, patient's

death during surgery and before the completion of the intervention, laryngoscopy lasting for more than 15 seconds, and more than one attempt for laryngoscopy.

The required sample size for the study was determined based on the sample size estimation formula in prevalence studies. Considering a confidence level of 95%, a test power of 80%, a prevalence of 0.05 for hemodynamic disorders in patients classified as ASA class II or higher (due to the absence of similar research), and a minimum significant difference of 0.3 between the groups, the sample size was estimated to be 44 patients. However, for more certainty, we decided to study 45 patients in each group. Convenience sampling was performed in this study. Patients were evaluated based on their time of visit and were included in the study if they met the inclusion criteria. Randomization was performed using the random allocation software. The total sample size and the number of groups were entered into the software. The software output included a list, which randomly assigned patients into two groups based on their numbers. The patients were divided into two study groups based on their time of visit, as indicated in the aforementioned list, until the required sample size was reached for each group.

For blinded sampling, the patients, the data collector, and the statistical analyst were all unaware of the type of drug administered to the patients. The drugs were prepared in identical, coded syringes by a member of the operating room staff who was not involved in the study. They were then handed over to the project manager, who was aware of the contents of the syringes for administration. Meanwhile, the individual responsible for collecting the results was kept unaware of the type of drug injected. Data analysis was performed by the statistical consultant using the mentioned codes. After the results were determined and the statistical analysis was conducted, the codes were revealed. Subsequently, the study findings were compiled.

The researcher attended the preanesthetic assessment clinic of Al-Zahra Hospital after making the necessary coordination. Patients who were candidates for surgery were examined, and those who met the eligibility criteria were selected. The study plan was then thoroughly explained to these patients, and if they agreed to participate in the study, written consent was obtained from them. In the operating room, after monitoring and preparing the equipment and recording vital signs and arterial oxygen saturation (SPO2) percentage, the patients were divided into two groups using the random allocation method.

First, 2 µg/kg of fentanyl, 0.6 mg/kg of atracurium, 1.5 mg/kg of lidocaine, and 2 mg of midazolam were intravenously administered to all patients two minutes before laryngoscopy. For the first group, 0.3 mg/kg of etomidate was administered at a rate of 0.1 mg/kg/min. For the second group, a combination of propofol (1.5 mg/kg) at a rate of 0.5 cc/s and ketamine (0.5 mg/kg) at a rate of 0.5 mg/kg/min were injected separately. Approximately three minutes later, ventilation was performed using a face mask, followed by tracheal intubation. After bilateral auscultation and confirmation of correct placement, the tracheal tube was secured.

In both groups, measurements were taken in several intervals: right before the injection of the anesthetic drug, immediately after the injection of the anesthetic drug, right before laryngoscopy, and at 1, 3, 5, and 10 minutes after laryngoscopy. The measured and documented parameters included systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, heart rate, and SPO2 percentage. If the patient's systolic blood pressure reached below 90 mmHg after anesthesia induction, 5 mg of ephedrine was injected intravenously to the patient and recorded in the patient's form. Additionally, if a patient’s blood pressure exceeded 160/90 mmHg (provided that the heart rate was >80 bpm), labetalol was injected intravenously at a dose of 5 mg. It is worth noting that the blood pressure of all patients was measured from the left hand using a brachial sphygmomanometer, and the patient’s blood pressure was assessed non-invasively.

The study monitored and recorded the occurrence of hemodynamic disorders during surgery, including hypotension, hypertension, tachycardia, and bradycardia (a change of >30% from the baseline). If necessary, medications to increase or decrease blood pressure were administered again, and the used amount of drugs was documented in the form. If the patient’s heart rate fell below 40 bpm, two ampoules of 0.5mg atropine were administered. Moreover, changes in ST segment depression were assessed by comparing leads 2 and 5. If any changes were observed, lead 12 was also taken into consideration. Other essential information, such as the duration of the operation, the duration of anesthesia, the time of endotracheal tube removal, the length of recovery, the administration and dosage of labetalol and ephedrine, and the dosage of other drugs used, was all documented in each patient’s form.

After collecting data, it was entered into SPSS Version 26 and analyzed. The changes in hemodynamic parameters during surgery and recovery were compared using repeated measures analysis of variance (ANOVA). Chi-square test was also performed to compare nominal data between the groups, and t-test was used to compare quantitative data between variables. All tests were analyzed at a significance level of <0.05.

Results

In this study, a total of 90 patients undergoing laryngoscopy were divided into two groups of 45 each. One group received etomidate, while the other group was administered Ketofol. During laryngoscopy, no patient was excluded from the study due to unwanted complications, and data analysis was performed on 90 patients (Figure 1).

According to (Table 1), there were no significant differences between the two groups in terms of demographic and clinical variables ($P<0.05$).

According to (Table 2), the examination of hemodynamic parameters up to 10 minute after laryngoscopy showed that none of these parameters were significantly different between the two groups, while immediately after anesthesia induction, heart rate and blood pressure were found to be significantly different. From the 1st minute up to the 10th minute after laryngoscopy, all the mentioned parameters were significantly different between the three groups, and the control group exhibited higher heart rate and blood pressure compared to the other groups. However, there was no significant difference in terms of SPO2 among the two groups in any given interval.

The intra-group analysis of the data revealed that the changes in hemodynamic parameters during the study were significantly different in all three groups. Also, according to the inter-group analysis, the changes in hemodynamic parameters were significantly different between the three groups. Moreover, the results showed significant differences between the two study groups regarding heart rate in the 3rd and 5th minutes after laryngoscopy, systolic blood pressure in the 1st and 3rd minutes, and diastolic blood pressure prior to laryngoscopy and in the 1st minute after laryngoscopy.

There were also no significant differences in nausea (P=0.41), vomiting (P=0.38), hypoxia (P=0.49), tachycardia (P=0.36), bradycardia (P=0.99), pain (P=0.67) and, shivering (P=0.19) between the two groups, as shown in (Table 3).

According to the intra-group analysis, a significant difference was observed in the pattern of change across all parameters in both study groups. Also, in the inter-group analysis, there was a significant difference in the pattern of change for heart rate (P=0.038), systolic blood pressure (P=0.021), and diastolic blood pressure (P=0.012) between the two study groups. However, changes in the mean blood pressure and SPO2 were not significantly different between the two study groups. The patterns of change in hemodynamic parameters are illustrated in (Figure 2).

As shown in Table 4, there was a significant difference in the average laryngoscopy time between the two study groups, with the duration being longer in the Ketofol group. Also, the duration of extubation and the length of recovery were significantly different between the two study groups. Two patients from the etomidate group and 16 patients from the Ketofol group received ephedrine (4.6% vs. 35.6%), and the difference between the two groups was significant (P<0.001). The average dose of ephedrine administered in the two groups was 17.5±17.7 mg and 13.1±14.8 mg, respectively; however, the difference between the two groups was not significant (P=0.70).

In the etomidate group, four individuals (8.9%) received labetalol, while in the Ketofol group, nine patients (20%) were administered labetalol; however, the difference between the two study groups was not statistically significant (P=0.23). The administered dose of labetalol in the two groups was 15±10 mg and 5.56±0.56 mg, respectively, and the difference between the two groups was not significant (P=0.79). Additionally, in the etomidate and Ketofol groups, two and five patients (4.4% vs. 11.1%) received total nucleated cells (TNCs), respectively, while the difference between the two groups was not significant (P=0.43). The average dose of TNC administered to the two groups was 350±70.7 mg and 180±182.3 mg, respectively. However, the difference between the two groups was not statistically significant (P=0.28).

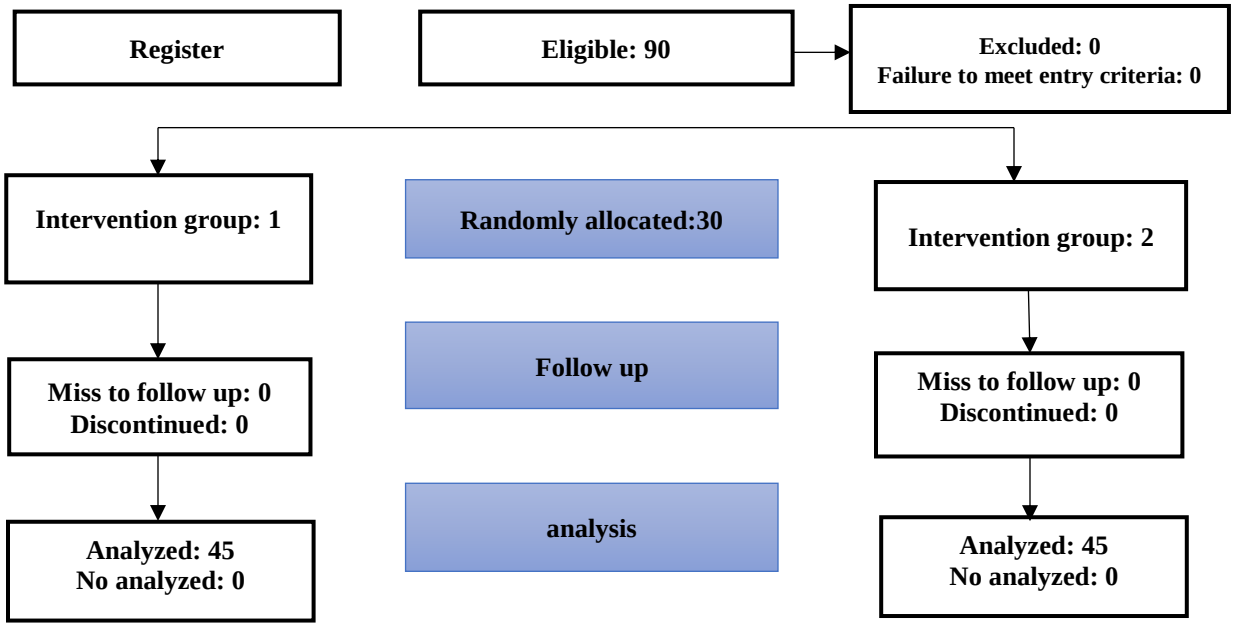


Figure 1- Study Flow Chart

Table 1- Frequency distribution of demographic and clinical characteristics

Variables		Groups		P value
		Etomidate	Ketofol	
Mean(±SD) of age (year)		73.6 ± 5.4	73.9 ± 6. 8	0.82
Mean(±SD) of weight(Kg)		73.9 ± 8.4	76.3 ± 10.5	0.24
Mean(±SD) of BMI(kg/m2)		26.59 ± 2.50	26.28 ± 3.23	0.62
Sex	Male	23(51.1)	25(55.6)	0.67
N(%)	female	22(48.9)	20(44.4)	
ASA	II	39(86.7)	36(80)	0.21
	III	6(13.3)	6(13.3)	
	IV	0(0)	3(6.7)	
Smoking		10(22.2)	18(40)	0.07

Table 2- Mean changes of hemodynamic parameters before until 10 mints after laryngoscopy in the two groups

Variables	Time	Groups		P value*
		Etomidate	Ketofol	
Heart rate (beat per min)	Before injection	78.8 ±10.9	78.4 ± 8.9	0.83
	Immediately after injection	82.8 ±12.3	90.3 ± 19.3	0.031
	Before laryngoscopy	84.5 ± 16.4	89.7 ±15.3	0.13
	1 min later	86.2 ± 14.5	89.5 ± 15.1	0.29
	3 min later	81.1 ± 13.9	88.2 ± 14.7	0.021
	5 min later	80.3 ± 11.8	86.3 ± 12	0.020
	10 min later	77.8 ±11.8	82.6 ± 15.5	0.10
	P**	<0.001	0.001	0.038***
Systolic blood pressure (mmHg)	Before injection	139.6 ± 23.6	138.6 ± 17.6	0.30
	Immediately after injection	124 ±25.9	110 ±23	0.008
	Before laryngoscopy	127.3 ± 19.8	116.2 ± 25	0.021
	1 min later	136.4 ±24.7	121.4 ±27.6	0.008
	3 min later	135 ±22	125.1 ±20.8	0.032
	5 min later	128.9 ± 19.5	126 ± 17.8	0.46
	10 min later	131.1 ± 17.3	126.5 ± 11.7	0.14
	P**	<0.001	<0.001	0.021***
diastolic blood pressure (mmHg)	Before injection	90.8 ± 15.6	88.7 ± 13.4	0.50
	Immediately after injection	77.5 ± 16.8	67.3 ± 18.3	0.007
	Before laryngoscopy	84.4 ± 16.4	73 ± 17.9	0.002
	1 min later	90.3 ± 15.3	82 ± 17	0.016
	3 min later	88.3 ± 12	84 ± 15.8	0.15
	5 min later	84.5 ± 14.4	84.7 ± 14.1	0.95
	10 min later	86.6 ± 13	83.8 ± 11.2	0.28
	P**	<0.001	<0.001	0.012***
Mean arterial pressure (mmHg)	Before injection	107.7 ±19.7	103.4 ± 14	0.23
	Immediately after injection	93.4 ± 21.2	82 ± 19.4	0.009
	Before laryngoscopy	100 ± 21.1	86.3 ± 20	0.002
	1 min later	106.2 ± 21.5	96. ± 19.3	0.019
	3 min later	99.3 ± 17.1	97.4 ± 14.3	0.06
	5 min later	99.3 ± 17.1	97.4 ± 14.3	0.58
	10 min later	101.4 ± 14.7	97.1 ± 11	0.12
	P**	<0.001	<0.001	0.009***
Mean O2 saturation (%)	Before injection	94.8 ± 1.7	94.5 ± 21.2	0.23
	Immediately after injection	96 ± 1.8	95.5 ± 1.7	0.24
	Before laryngoscopy	96.6 ± 1.8	96.7 ± 1.6	0.76
	1 min later	98.2 ± 1.6	98 ± 1.3	0.42
	3 min later	98.5 ± 1.5	98.4 ± 1.1	0.81
	5 min later	98.6 ± 1.5	98.8 ± 0.96	0.67
	10 min later	98.8 ± 1.3	98.7 ± 1	0.71
	P**	0.001	<0.001	0.72***

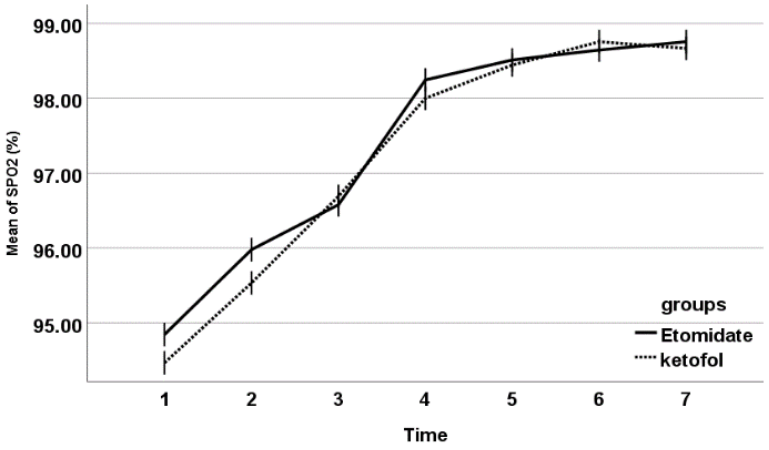
*Significant level of difference between three groups at each point of time according to one-way analysis of variance test
**Significant level of changes within each group according to repeated measures ANOVA
**Significant level of changes between the three groups according to repeated measures ANOVA

Table 3- Frequency distribution of occurrence of hemodynamic disorder in the two groups

Variable	Groups		P value
	Etomidate	Ketofol	
Nausea	16(35.6)	19(42.2)	0.67
Vomiting	5(11.1)	8(17.8)	0.55
Hypoxia	0(0)	2(4.4)	0.49
Tachycardia	12(26.7)	16(35.6)	0.36
Bradycardia	1(4.4)	1(2.2)	0.99
Postoperative pain	29(64.4)	26(57.8)	0.67
Postoperative shivering	13(28.9)	20(44.4)	0.19

Table 4- Mean and standard deviation of laryngoscopic time, operation time, anesthesia time, extubation time and recovery time in the two groups

Variables	Groups		P value
	Etomidate	Ketofol	
laryngoscopic time	7.2 ± 1.8	7.9 ± 1.6	0.043
operation time	118 ±30.9	107.6 ±30.4	0.11
anesthesia time	139.1 ±34.9	125.8 ±31.2	0.06
extubation time	21.1 ±8.5	25.7 ±11	0.029
recovery time	68.9 ± 10.3	62.7 ± 12.9	0.014



1: before injection, 2: immediately after injection, 3: before laryngoscopy, 4: One min later, 5: Three min later, 6: Five min later, 7: Ten min later

Figure 2-Mean of SPO2 in 7 times in the two groups

Discussion

Traumatic Hemodynamic disorders represent a significant challenge in tracheal intubation, as they can lead to complications, such as tachycardia, hypertension, and arrhythmia, by stimulating the central nervous system. Therefore, numerous studies have been undertaken with the aim of minimizing the incidence of these disorders. Etomidate, propofol, and ketamine are frequently prescribed for anesthesia induction and are commonly used in patients, particularly the elderly. However, the desired control over blood pressure and heart rate has not been fully achieved during laryngoscopy.

While numerous studies have been conducted to stabilize hemodynamics and reduce postoperative complications in patients, no study has yet compared the effects of etomidate and ketamine-propofol combination (Ketofol). Since the use of intravenous anesthetics may be associated with serious risks and complications in the elderly and can lead to various complications, such as hemodynamic disorders during laryngoscopy, the present study aimed to compare the effect of Ketofol with that of etomidate on the hemodynamic status of patients classified as ASA class II or higher. Based on the preliminary findings of this study, there was no significant difference between the two groups receiving etomidate and Ketofol in terms of demographic and clinical characteristics, baseline and hemodynamic variables, and the duration of laryngoscopy, and these variables had no confounding effects on the outcome of the study. Therefore, the observed differences between

the two groups were probably attributed to the type of drug used.

In this study, an examination of hemodynamic parameters up to 10 minutes after laryngoscopy revealed significant differences in heart rate, systolic blood pressure, and diastolic blood pressure between the two study groups. Based on the findings, the group receiving Ketofol exhibited a higher heart rate and lower blood pressure compared to the etomidate group. Therefore, it seems that the use of Ketofol is preferable to etomidate in maintaining the hemodynamics of elderly patients during laryngoscopy. Meanwhile, there was no significant difference between the two study groups in terms of hemodynamic disorders, such as tachycardia, bradycardia, hypotension, and hypertension.

In a study conducted by Sergi demonstrated a significant association between pre-frailty and the risk of incident cardiovascular disease. This suggests that targeting pre-frailty as a potentially reversible risk factor for cardiovascular disease in the elderly could have significant implications [21].

In an article conducted by Pathanon et al., it was found that both Ketofol and propofol-fentanyl combination (Fenofol) are effective sedative options for colonoscopy. Nevertheless, Ketofol provided superior sedation and required less airway management than Fenofol. On the downside, it was associated with a higher incidence of hallucinations and nightmares [22]. In another study by Baradari et al., the impact of Ketofol and etomidate on the postoperative outcomes and hemodynamics of patients undergoing coronary artery bypass grafting (CABG) was examined. In this study, a total of 84 patients were divided into three groups of Ketofol, etomidate, and control. It was observed that the decrease in heart rate and blood pressure during laryngoscopy was more pronounced in the Ketofol group compared to the etomidate group [23].

Additionally, in a study by Sanri et al., two groups of patients undergoing laryngoscopy were compared. One group (n=55) received Ketofol, while the other group (n=57) received an etomidate-fentanyl combination (Etofen). The results of this study indicated that patients who received Ketofol exhibited better hemodynamic stability and a lower incidence of hemodynamic disorders during surgery [24]. Moreover, in a study by Hosseinzadeh et al., the effects of Ketofol and propofol/etomidate-lipura combination (Etofol) on the hemodynamic stability of elderly patients during laryngoscopy were investigated. In this study, 30 patients received Ketofol, while 32 patients received Etofol. According to their findings, the hemodynamic and respiratory variables, including blood pressure, heart rate, and SPO2 percentage, did not differ significantly between the two groups during laryngoscopy. Also, no significant difference was observed between the groups post-intubation and six minutes thereafter [25]. Overall, ketamine and propofol are recognized as having minimal side effects on the patients' hemodynamics, and the combination of these two drugs has been found to mitigate the negative effects on hemodynamic changes.

Limitations

Considering the limitations of this study, such as the small sample size, multiple exclusion criteria, and age restriction, further relevant research is highly recommended.

Conclusion

The results of the present study revealed that Ketofol resulted in better regulation and stability of blood pressure and heart rate in patients undergoing endotracheal intubation, compared to etomidate alone. Also, Ketofol may be superior in maintaining hemodynamic stability. However, considering the limitations of this study, including the small sample size, it is suggested to conduct further research in this area to substantiate these findings.

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