Original Article

A Comparative Study of the Effect of Low-Dose Epinephrine and Ketamine on Rapid-Sequence Endotracheal Intubation by the Priming Dose Method of Cisatracurium in Patients under General Anesthesia

Hamid Hajigholam Saryazdi[1], Azim Honarmand[2], Behzad Nazemroaya[3], Pouyan Naderi Afshar[4]

[1]Department of Anesthesiology, School of Medicine, Anesthesiology and Critical Care Research Center, Kashani Hospital, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Anesthesiology, School of Medicine, Anesthesiology and Critical Care Research Center, Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Anesthesiology, School of Medicine, Anesthesiology and Critical Care Research Center, Al-Zahra Hospital, Feiz Hospital, Isfahan University of Medical Sciences, Isfahan, Iran, [4]Department of Anesthesiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Low-dose ephedrine and ketamine may accelerate the onset time of action of neuromuscular blocking agents. We studied the effect of ephedrine and ketamine and cisatracurium priming on endotracheal intubation conditions and the onset time of action of cisatracurium.

Materials and Methods: The study was a double-blind clinical trial performed on American Society of Anesthesiologists (ASA) class 1 and 2 patients, who were candidates for general anesthesia. In total, 120 patients were entered into the study and were divided into 4 groups, E, K, E + K, and N. The first group was given 70 mcg/kg ephedrine (E group), the second group was given 0.5 ml/kg ketamine (K group), the third group was given the same amount of ketamine plus ephedrine (E + K group), and the fourth group was given the same volume of normal saline (control group); a single dose of 0.1 mg/kg cisatracurium was given, and intubating conditions were evaluated at 60 seconds after cisatracurium administration.

Results: The mean Cooper score based on the response to laryngoscopy, the position of the vocal cords, and the movement of the diaphragm of patients in the control group with a mean of 2.53 ± 1.07 was significantly lower than in the three groups of E, K, and E + K with the means of 4.47. 1.17, 4.53 ± 1.14, and 7.63 ± 1.42, respectively (P value < 0.001). In the (E + K) group, it was significantly higher than in the two other drugs alone (P value < 0.001). The two groups of E and K alone were not significantly different from each other (P value = 0.997). The means of hemodynamic parameters were not significantly different in any of the groups (P value > 0.05).

Conclusion: According to the results of the present study, the use of low-dose ephedrine and ketamine alone can improve intubation conditions. In addition, the combined use of these drugs not only had any Positive effect on patients' hemodynamic parameters but also greatly improved intubation conditions.

Keywords: Cisatracurium, ephedrine, fast tracheal intubation, ketamine, priming method

Address for correspondence: Dr. Behzad Nazemroaya, Department of Anesthesiology, School of Medicine, Anesthesiology and Critical Care Research Center, Al-Zahra Hospital, Feiz Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: behzad_nazem@med.mui.ac.ir
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Introduction

Ephedrine is a sympathomimetic (vasopressor) drug, which is used both in children and adults in the treatment of hypotension or orthostatic hypotension. It is also used to treat acute and severe bronchospasm as a bronchodilator

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in symptom therapy of asthma and in symptom relief in case of reversible bronchospasm in chronic bronchitis, emphysema, and other obstructive lung diseases. It can also be used as an anti-congestive medication in case of nasal congestion. Additionally, it is given in closed-angle glaucoma (narrow-angle glaucoma), but it is contraindicated in general anesthesia using halothane and psychogenic disorders. Furthermore, in cases of hypertension, in geriatric patients, diabetic patients, and those with a history of cardiovascular diseases, it should be used with caution.[1]

Ketamine is a medication which suppresses the central nervous system and acts as an anesthetic.[2] Ketamine is a phencyclidine analogue that acts by inhibiting the n-methyl-d-aspartate receptor complex and inhibits the transmission of pain signals to the limbic system by blocking the glutamate receptors in the thalamic area of the brain. The medical use of ketamine is by intravenous (IV) or intramuscular (IM) injection. Some of the complications of this drug include delirium on awakening, lucid dreams, and dissociative delusional experiences which have limited its use. The unique characteristics of this medication, including deep analgesia and the stimulation of the sympathetic nervous system while causing a minimal amount of respiratory system suppression, make it an important alternative to other anesthetic drugs.[3,4]

Propofol is also a medication which can be used as an intravenous sedative or anesthetic. It is used as an induction medication in anesthesia or to maintain anesthesia and in lower doses to sedate adult patients under mechanical ventilation in the intensive care unit. The maximum duration of action of this medication is about 2 minutes and in some cases between 5 and 10 minutes. Some of the side effects of this drug include decreased heart rate, decreased blood pressure, pain at the injection site, and suppressed respiration (apnea). In addition, some of the more serious complications of this medication include infection from a previously opened container of this drug, addiction, and the syndrome from prolonged use. In contrast, this medication does not possess analgesic properties; therefore; it must be used simultaneously with opioids such as morphine. Propofol has anti-convulsive and anti-emetic characteristics with a rapid recovery time.[4]

However, neuromuscular relaxing agents are divided into 2 groups; non-depolarizing and depolarizing drugs. The mechanism of action and limitations of these two groups greatly affect the decision on the choice of such medications for the induction of anesthesia.[5] Succinylcholine is the neuromuscular blocking agent of choice in rapid-sequence anesthesia.[6] It is a short acting neuromuscular blocking agent which exerts its muscle relaxing activity by acetylcholine-like properties which can last for a few minutes.[7] Some of the complications that have been identified for succinylcholine include increased release of potassium from skeletal muscles in burn patients,[8] patients with trauma to skeletal muscles,[9] patients with trauma to the central nervous system,[10] and those with spinal cord injuries,[11,12] peripheral nerve injuries,[13] and muscle changes due to inactivity.[14,15] The subsequent increase in serum potassium levels may cause some problems in patients, including ventricular arrhythmias and cardiac arrest because; when succinylcholine is used, the depolarization process can cause an increase in serum potassium levels.[16] Such patients can therefore suffer from arrhythmias and, ultimately, cardiovascular collapse.[17] Furthermore, the use of succinylcholine in the presence of specific conditions, such as a deficiency of the pseudocholinesterase enzyme, the use of choline-esterase-inhibiting drugs, and severe neuromuscular disorders, can potentially increase the risk of anesthesia.[18] However, cisatracurium (with the commercial name Nimbex) is the R cis-R´ isomer of atracurium.[19] Cisatracurium and atracurium are both non-depolarizing neuromuscular blocking agents, with cisatracurium being 3 times more potent than atracurium.[20] Cisatracurium causes less histamine release, which is the main complication of atracurium use.[21,22] Cisatracurium is mostly used as a neuromuscular blocking agent during anesthesia induction to facilitate endotracheal intubation, so it is used in various kinds of surgeries.[23] Cisatracurium is frequently used during anesthesia for surgeries performed to repair congenital heart conditions.[24,25] This medication is metabolized spontaneously in the physiological temperature and pH of the body by the Hoffman elimination mechanism and is subsequently metabolized into a number of conjugated metabolites.[26] Therefore, the metabolism of cisatracurium usually takes place in the plasma and tissues. Although it is metabolized using the Hoffman mechanism, plasma esterase also has a role in hydrolyzation of this drug.[27]

As a result, finding a medication which does not have the side effects of succinylcholine and that also meets our expectations in providing a suitable neuromuscular blockade in the induction of anesthesia prompted us to take up cisatracurium, which is generally considered to be a medication with marginal complications. Although cisatracurium has a medium duration of onset, by utilizing a minimal initial dose of cisatracurium as priming dosage and adding ephedrine or ketamine to this drug and subsequently administering the complementary dose, endotracheal intubation was performed after 1 minute of anesthesia induction. Based on the fact that no similar study has yet been performed in this regard, the objective of this study was to assess the complications of ephedrine and ketamine and compare the effects of these two drugs which could accelerate the onset time of the neuromuscular blocking agents and improve the conditions for endotracheal intubation.

Materials and Methods

This double-blind controlled clinical trial study was performed on 120 patients for surgery under general anesthesia. These patients were selected by non-randomly available methods.

Inclusion criteria were patients who were candidates for elective surgery, aged between 18 and 65, under the American Society of Anesthesiologists (ASA) class one and two classifications and those who had given consent for entering

the study. Having an allergic reaction to the medications caused the patient to exit the study. Also, the exclusion criteria were moderate to severe allergy and non-cooperation of the patient to continue the study.

After obtaining the code of ethics from the Isfahan University of Medical Sciences (approval code: IR.MUI.REC.1398.644) and the code of clinical trial (registered code: IRCT20160307026950N23) and written consent from patients eligible to enter the study, the basic information including age, sex, height, and weight were recorded first.

Then, the patients were divided into four groups using random allocation software, and an IV line was provided for all patients. Then, it was applied to each patient, and monitoring devices such as the heart rate (HR), SPO2, and non-invasive blood-pressure monitoring (for measuring systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MAP)) devices were attached to the patients.

Then, before induction of anesthesia, the desired intervention was performed for each patient. In the first group, 70 mcg/kg epinephrine (manufactured by Darooyab Corp., Iran) was used intravenously (E group). In the second group, 0.5 mg/kg of ketamine (manufactured by Darooyab Corp., Iran) was administered intravenously (K group). In the third group, 0.5 mg/kg ketamine (manufactured by Darooyab corp., Iran) combined with 70 mcg/kg epinephrine (manufactured by Darooyab Corp., Iran) was used intravenously (E + K group). In the fourth group, normal saline was applied (control group) [Figure 1].

It should be noted that to observe the blinding conditions, 4 packages of drugs were prepared in the same 5 ml syringes identified with A, B, C, and D labels and were given to the anesthesiologist daily. Thus, the intervener and the patient had no information about the type of intervention. In addition, the data collector and statistician did not have any information on the type of intervention in each group until the end of the study.

After injection of the intervention, patients underwent general anesthesia. For induction of anesthesia, 1 mg of midazolam (produced by Caspian-Tamin Company, Iran) and 100 mcg of fentanyl (produced by Darooyab Company, Iran) and, after that, 10 mg of propofol (produced by Darooyab Company, Iran) were injected. Subsequently, atracurium (made by Abooreyhan Pharmaceuticals, Iran) at a dose of 0.05 mg/kg was administered. It was asked of the patient to report any signs of diplopia when it occurred, or when nystagmus was seen in the patients' eyes, 12 mg/kg of propofol was administered immediately, after which 0.1 mg/kg of cisatracurium was injected, and then, the time was recorded using a chronometer.

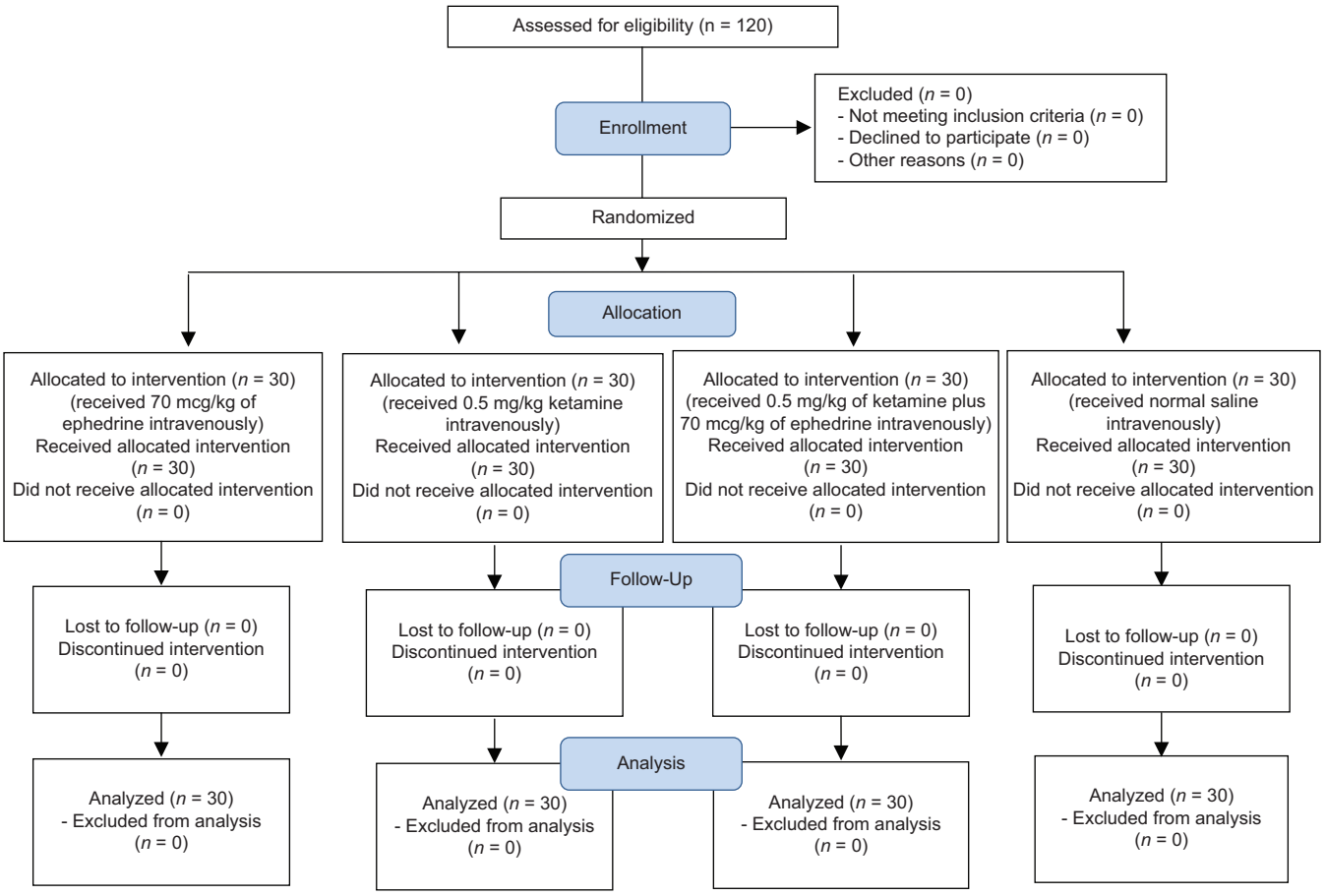

Figure 1: Consort flowchart of patients

Patients' hemodynamic parameters including SBP, DBP, MAP, HR, and SPO2 were evaluated and recorded before the intervention, immediately after the intervention and at 15, 30, 45, and 60 minutes after the intervention. Rapid-sequence endotracheal intubation from the Cooper score system criterion was also used. One minute after the intervention, the laryngoscopy response rate, the position of the vocal cords, and the movement of the diaphragm based on a score of 0 (impossible to open), 1 (opens with difficulty), 2 (moderate opening), and 3 (easy opening) were determined, and finally, the total score was obtained from 0 to 9. A score from 8 to 9 was seen as excellent, 6 to 7 was good, 3 to 5 was weak, and 0 to 2 was poor. Excellent and good conditions were considered suitable for tracheal intubation.[28]

Statistical analysis

Finally, the collected data were entered into SPSS software (Ver. 26). Data are shown as mean ± standard deviation (SD) or *n* (%). At the level of inferential statistics, according to the result of Kolmogorov–Smirnov indicating the normal distribution of data, one-way analysis of variance (ANOVA) was used to compare the mean of quantitative variables between the four groups and Tukey's post-hoc test was used to compare the two pairs. Also, to compare the mean changes of quantitative variables with time in each groups, the repeated-measure ANOVA was used. In addition, Chi-square test was used to compare qualitative variables between the four groups. In all analyzes, a significance level of less than 0.05 was considered.

Results

In the present study, there were 20 (66.7%) males and 10 (33.3%) females with a mean age of 31.93 ± 12.62 years in the E group, 24 (80%) males and 6 females (20%) with a mean age of 35.27 ± 14.74 years in the K group, 26 (86.7%) males and 4 (13.3%) females with a mean age of 32.33 ± 10.14 years in the group receiving combination therapy of E + K, and 21 (70%) males and 9 (30%) females with a mean age of 14.52 33 33.43 years in the control group (*P* value > 0.05) [Table 1].

However, the mean hemodynamic parameters of patients including HR, SBP, DBP, MAP, and SPO2 before the intervention, immediately after the intervention, and at 15, 30, 45, and 60 minutes after the intervention were not significantly different between the four groups (*P* value > 0.05) [Table 2].

To evaluate the effect of the intervention on rapid-sequence endotracheal intubation, Cooper score system criterion was used to score the response to laryngoscopy, the position of the vocal cords, and the movement of the diaphragm. Finally, the mean Cooper score in the control group with a mean of 2.53 ± 1.07 was significantly lower than in the three groups of E, K, and E + K with a mean of 4.47 ± 1.17, 4.53 ± 1.14, and 7.63. 1.42, respectively (*P* value < 0.001). However, in contrast, there was no significant difference between the two groups of E and K alone (*P* value = 0.997). The mean of Cooper score in the E + K group was significantly higher than using either drug alone (*P* value < 0.001). In addition, in evaluating the frequency distribution of this criterion based on excellent, good, poor, and very poor, it was shown that in the first minute after injection of the ketamine and epinephrine combination, there was the highest response rate in excellent condition with 60%; while the other groups did not have the excellent condition, and the highest percentage of poor condition was in the control group compared to the other groups (*P* value < 0.001) [Table 3, Figure 2].

Discussion

Regarding the variable of heart rate, the effect of time was significant (*P* < 0.001), in which based on Figure 1 and Table 3,

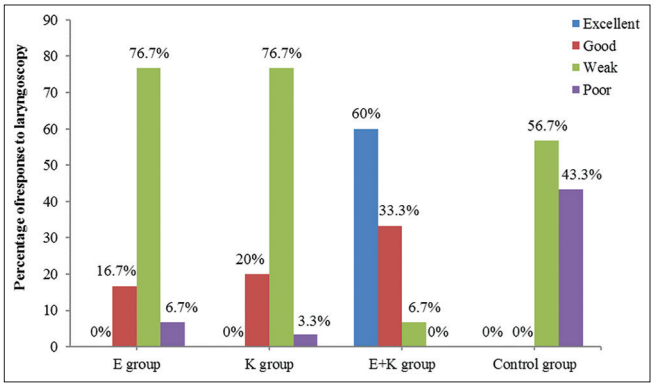

Figure 2: Frequency distribution of intubating conditions based on the Cooper score system criteria in four groups

Table 1: Characteristics of patients in four groups

Variable	E group (*n*=30)	K group (*n*=30)	E + K group (*n*=30)	Control group (*n*=30)	*P**
Sex					
Man	20 (66.7)	24 (80)	26 (86.7)	21 (70)	0.265**
Female	10 (33.3)	6 (20)	4 (13.3)	9 (30)	
Age, year	31.93±12.62	35.27±14.74	32.33±10.14	33.43±14.52	0.763
Height, cm	1.70±0.09	1.69±0.07	1.73±0.10	1.70±0.08	0.141
Weight, kg	74±17.59	69.47±12.32	77±15.76	71.73±11.61	0.226
Recovery time, minute	60±18.10	60.67±16.28	65.50±15.56	61.33±14.50	0.551
Headache	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	0.585**

*One-way ANOVA test. **Independent t-test. E group: ephedrine group; K group: ketamine group; E + K group: ephedrine + ketamine group

Table 2: Comparison of mean hemodynamic parameters of patients between four groups

Variable	E group ($n=30$)	K group ($n=30$)	E + K group ($n=30$)	Control group ($n=30$)	*P*
Heart rate					
Baseline	92.69±19.11	84.96±18.30	87.37±14.13	84.11±22.25	0.575
Before intervention	93.81±18.52	88.39±18.50	89.93±16.29	88.93±16.10	0.863
T0	100.42±19.69	96.52±21.44	99.30±20.68	92.54±17.02	0.973
T15	92.62±24.17	92.83±16.05	90.33±22.85	85.00±16.51	0.371
T30	90.12±20.38	87.91±16.81	83.22±19.46	83.93±20.04	0.255
T45	89.19±18.92	82.78±15.42	82.44±17.74	86.32±19.07	0.530
T60	87.69±18.34	84.52±24.09	85.41±23.98	82.79±17.28	0.131
P	<0.001	0.003	<0.001	0.004	
Mean blood pressure					
Baseline	94.58±11.02	97.26±13.41	94.56±13.13	93.32±12.82	0.550
Before intervention	92.04±15.28	95.83±14.34	90.78±14.83	90.36±14.70	0.591
T0	95.19±19.38	99.13±14.38	96.89±21.55	93.57±15.25	0.186
T15	82.54±15.54	88.91±12.11	84.93±11.39	85.43±10.10	0.599
T30	84.12±16.28	82.83±14.73	86.96±12.69	86.54±12.60	0.386
T45	85.15±13.24	81.26±15.11	87.00±12.43	91.04±14.54	0.770
T60	79.42±25.11	82.96±17.12	85.78±14.13	86.43±13.73	0.371
P	<0.001	<0.001	<0.001	<0.001	
SPO2					
Baseline	98.92±1.02	98.23±2.60	98.19±2.40	98.54±1.07	0.179
Before intervention	98.92±1.02	98.50±1.79	98.50±1.61	98.65±0.94	0.560
T0	99.04±0.66	98.50±1.82	98.65±1.65	98.96±0.60	0.411
T15	99.08±0.63	98.68±1.36	98.77±1.31	99.00±0.63	0.274
T30	99.27±0.60	98.86±0.99	98.92±0.98	99.04±0.53	0.726
T45	99.23±0.59	99.05±0.65	99±0.69	99.08±0.63	0.506
T60	99.19±0.63	99.00±0.69	99.08±0.69	99.04±0.66	0.321
P	0.012	0.008	0.022	<0.001	
Systolic blood pressure					
Baseline	132.63±18.53	127.30±15.04	128.20±18.09	127.50±16.48	0.585
Before intervention	123.70±30.26	126.10±15.75	127.77±29.22	127.00±18.25	0.924
T0	124.67±33.04	123.73±27.62	137.30±25.75	124.10±23.27	0.171
T15	116.00±18.69	117.63±16.53	112.80±20.69	115.90±16.56	0.776
T30	117.03±16.86	116.73±19.42	119.03±18.09	114.77±16.57	0.833
T45	117.90±16.22	114.04±18.11	119.70±14.67	117.60±17.60	0.638
T60	117.93±16.54	115.21±18.58	114.30±15.60	118.12±19.18	0.811
P	0.005	0.006	<0.001	0.006	
Diastolic blood pressure					
Baseline	77.88±10.23	82.70±12.24	79.56±11.29	77.32±11.78	0.275
Before intervention	74.62±14.98	80.57±12.55	77.11±12.56	76.61±12.84	0.463
T0	77.31±19.69	82.39±13.50	82.11±21.65	79.25±14.29	0.090
T15	67.73±14.95	76.09±12.06	68.81±11.24	71.82±9.88	0.713
T30	68.69±16.21	68.43±14.24	71.93±10.88	71.61±11	0.153
T45	68.15±13.33	66.35±14.41	70.85±11.80	70.57±17.76	0.075
T60	68.38±14.40	67.30±16.22	69.96±14.68	71.75±12.35	0.414
P	<0.001	<0.001	<0.001	<0.001	

E group: ephedrine group; K group: ketamine group; E+K group: ephedrine+ketamine group. T0: immediately after the intervention; T15: 15 minutes after the intervention; T30: 30 minutes after the intervention; T45: 45 minutes after the intervention; T60: 60 minutes after the intervention

the mean heart rate in all four groups after administration of the drug showed a decreasing trend. As can be seen in Figure 1, at all times, the E group had the highest and the control group had the lowest mean heart rate. Based on the fact of the significance of the interaction of time and group, the means in all groups were assessed and the reason for the significance of the difference in heart rate in the groups was the difference between the 30th and 60th minutes ($P=0.04$). During this time (between 30th to 60th minutes after anesthesia), the mean heart rate in the control group which was less than in the other groups before the 30th minute showed an increase, with the ephedrine and control groups showing a 1-unit decrease. However, the ketamine group showed a more severe decrease compared to the other groups during these 2 times. The effect

Table 3: Comparison of the mean Cooper score system in four groups

	E group ($n=30$)	K group ($n=30$)	E + K group ($n=30$)	Control group ($n=30$)
Cooper score	4.47±1.17	4.53±1.14	7.63±1.42	2.53±1.07
*P*1	<0.001		*P*4	0.997
*P*2	<0.001		*P*5	<0.001
*P*3	<0.001		*P*6	<0.001

1: Significance level resulting from comparing the mean Cooper score of the control group with group E. 2: Significance level resulting from comparing the mean Cooper score of the control group with group k. 3: Significance level resulting from comparing the mean Cooper score of the control group with the E+K group. 4: Significance level resulting from comparing the mean Cooper score of group E and group K. 5: Significance level resulting from comparing the mean Cooper score of group E and group E+K. 6: Significance level resulting from comparing the mean Cooper score of group K and group E+K

of the group was not significant ($P = 0.580$), which signifies the fact that the changes in the mean heart rate in the four groups did not show any significant differences.

With regards to the variable of SBP, the effect of time was significant ($P < 0.001$). By analyzing the difference in mean at different times, it was shown that this significance of difference was mostly because of the changes in the mean after the intervention till the 15th minute after induction of anesthesia, and during this time, there was a steep reduction in the trend in all four groups, especially in the drug combination group. However, from the 15th to the 60th minute after induction of anesthesia, there was a slight increase in the trend. Considering the significance of the interaction between time and group ($P = 0.007$), the means in various groups were analyzed, and the reason for the significance of difference in the mean in SBP in the groups was due to the difference at the time of anesthesia induction and after 15 minutes of anesthesia ($P = 0.03$). In that, before the time of intervention, the drug combination group had the highest mean compared to the 3 other groups, but after 15 minutes, the mean SBP in the drug combination showed a severe decrease compared to the 3 other groups and was the lowest at the 15 minutes' time compared to the other 3 groups. The changes in the mean in the combination group were different than in the other groups. The effect of the group was not significant ($P = 0.800$) which indicates that the mean in systolic pressure in the 4 groups was not significant.

It can be said about the DBP that the effect of time was significant ($P < 0.001$). By analyzing the difference in the mean during different times, this significance was found to be mainly due to the difference in the means at the time before the 30th minute in which there was a decline in all groups. However, after the 30th minute to 60 minutes after anesthesia, this decline decreased and became very mild (about a 1-unit decrease). Regarding the significance of the interaction of time and group, the means at different times in the various groups were analyzed, and the reason for the significance in the difference in diastolic pressure in the various groups was the changes after 30 minutes of anesthesia ($P = 0.04$). In that, before 30 minutes of anesthesia, the K group showed the highest mean compared to the three other groups, but after 30 minutes, the mean DBP in the K group showed a significant lowering compared to the other groups. The E group also showed a lower mean before 30 minutes of anesthesia compared to the other groups, but after 30 minutes, it slightly increased. The effect of the group was not significant ($P = 0.682$), which shows that the mean in changes in the DBP in the 4 groups was not significant.

Regarding the mean blood pressure variable, it was found that the effect of time was significant ($P < 0.001$), based on Figure and Table 3, the mean blood pressure in the 4 groups had a decreasing trend after drug administration. After assessment of the means in the various times in these groups, it could be said that this significance was mostly due to changes before the 30th minute of anesthesia, in as much that before this time, there was a decreasing trend in the 4 medicinal groups, but between the 30th and 60th minutes after anesthesia, this decreasing trend slowed down and was milder or showed a slight increase in some of the groups. Based on the significance of the changes according to the interaction of the time and group, we assessed the mean of the groups at different times and speculated that the reason for this significant difference in the various groups was due to the difference after 30 minutes after anesthesia. Accordingly, before the 30th minute after anesthesia, the K group had the highest mean compared to the three other groups, but after the 30th minute, the mean blood pressure in the K group decreased more compared to the other groups. The control group also had the lowest mean before the 30th minute compared to the other groups, but after the 30th minute and during the 45th and 60th minutes, it had the highest mean compared to the other groups. Therefore, the effect of group was not significant ($P = 0.857$), which denotes that the change in the mean blood pressure was not significant in the four groups.

Moreover, with regards to the changes in mean SPO2, the effect of time was significant ($P = 0.011$); based on Figure and Table 3, the mean in SPO2 in all four groups after the use of the medication showed an increasing trend. Analyzing the changes in the mean at different times showed that this change of means was mostly due to the changes before the 45th minute after anesthesia. In that, before this time, the trend increased significantly in the 4 groups, but from the 45th to the 60th minutes after anesthesia, this increasing trend was slower and milder or in some groups even decreasing. The effect of group ($P = 0.428$) and the interacting effect between time and group ($P = 0.956$) were not significant, which shows that the mean changes of SPO2 in the 4 groups were not significantly different.

Furthermore, comparison of the Cooper score is an appropriate method in evaluating the condition of endotracheal intubation for the patients under general anesthesia; similar studies such as the study by Labrada *et al.*,[29] about the conditions of endotracheal intubation in patients having laparoscopic

surgery under general anesthesia using rocuronium and succinylcholine, showed similar results. Therefore, it can be postulated that this parameter can be used to evaluate the suitable conditions for endotracheal intubation. In the present study, comparing the Cooper score between the 4 groups showed that the difference in score in these 4 groups was significant. The significance of the changes was because of the significant difference between the ephedrine group with the drug combination group, and the control groups, which were where − 3.167 and 1.933, respectively. This shows that the Cooper score in the ephedrine group was approximately 3 units less and about 2 units more than the drug combination and control groups, respectively. In addition, the differences between the mean in the K group with the drug combination control group were significant and were found to be −3.100 and 2, respectively, which shows that the Cooper score in the ketamine group was approximately 3 units less than the drug combination group and 2 units more than the control group.

In addition, other medications are also used in anesthesia, one of which is sodium thiopental, which is a general anesthetic of the barbiturate group.[15] This drug crosses the blood–brain barrier easily.[16] Sodium thiopental is used during brain ischemia and in cases of increased intracranial pressure. It causes a decrease in the activity of neurons in the brain,[17] and it is also used as the third-line medication in treating status epilepticus.[18] Sodium thiopental has some drawbacks too, including decreasing the seizure duration in electroconvulsive therapy (ECT), causing sinus bradycardia, and premature ventricular beats.[19] A study performed by Shahryari *et al.*[30] showed that both ketamine and propofol are medications which are effective to use during cardiac catheterization and are safe, but it is more prudent to use propofol in patients who are hemodynamically stable and under continuous cardiopulmonary monitoring.

In another study performed by the Anesthesiology Department of the Miami University in the United States of America, about the priming technique of cisatracurium, this medication was used at a dose of 0.01 mg/kg as the priming dose, and then different doses of cisatracurium (0.09, 0.14, and 0.19 mg/kg) were used as the intubation dose. Afterward, the conditions for endotracheal intubation were assessed and compared to a bolus dose of this medication. It was shown in the study that the conditions for intubation were not significantly different in the two groups, and in general, the priming technique caused a decrease in the onset of action of the non-depolarizing neuromuscular blocking agent and also the duration of action of this medication.[31]

Also, in another study by Mak *et al.*,[32] patients were allocated into 3 groups and compared. The first group received rocuronium at a dose of 0.09 mg/kg as a priming dose, the second group received cisatracurium at 0.15 mg/kg as a priming dose, and the third group received placebo. After 6 minutes, the two groups that received a priming dose were given cisatracurium at a dose of 0.135 mg/kg with the control group receiving 0.15 mg/kg of cisatracurium. The results demonstrated that there were no significant differences between the two groups regarding the onset time of muscular relaxation, but these two groups had a shorter onset time compared to the control group and intubation was performed at 50 to 90 seconds after muscle relaxant administration.

Additionally, in a study performed by the Department of Anesthesiology of Nigeria, a priming dose was compared with atracurium and succinylcholine for rapid-sequence endotracheal intubation. The results showed that the time of laryngoscopy based on clinical scores was 68 seconds in the control and 66 seconds in the intervention group. This was despite the fact that the assessment of musculoskeletal function in the control group was 62 seconds and 89 seconds in the intervention group.[33] The mentioned studies are in correspondence with our current study, but because of the lack of similar studies in this regard, there is a need for more extensive research about this subject.

Conclusion

The combined use of these drugs not only had any positive effect on patients' hemodynamic parameters but also greatly improved intubation conditions

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

The authors declare that they have no conflict of interest

References

1. Ibrahim L, Diazgranados N, Luckenbaugh DA, Machado-Vieira R, Baumann J, Mallinger AG, *et al*. Rapid decrease in depressive symptoms with an N-methyl-d-aspartate antagonist in ECT-resistant major depression. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:1155-9.
2. Hegazy MA, Hegazi RA, Hendawy SR, Hussein MS, Abdellateef A, Awad G, *et al*. Cardiac preconditioning effect of ketamine–dexmedetomidine versus fentanyl–propofol during arrested heart revascularization. Anesth Essays Res 2020;14:312-20.
3. Shiroma PR, Velit-Salazar MR, Vorobyov Y. A systematic review of neurocognitive effects of subanesthetic doses of intravenous ketamine in major depressive disorder, post-traumatic stress disorder, and healthy population. Clin Drug Investig 2022;42:549-66.
4. Abram SV, Roach BJ, Fryer SL, Calhoun VD, Preda A, van Erp TG, *et al*. Validation of ketamine as a pharmacological model of thalamic dysconnectivity across the illness course of schizophrenia. Mol Psychiatry 2022;27:2448-56.
5. Girish K, Gangadhar BN, Janakiramaiah N. Ect in neurological counditions. Indian J Psychiatry 2002;44:228-239.

6. Andrade C, Shah N, Tharyan P, Reddy MS, Thirunavukarasu M, Kallivayalil RA, *et al*. Position statement and guidelines on unmodified electroconvulsive therapy. Indian J Psychiatry 2012;54:119-33.
7. Anderson TA, Fuzaylov G. Perioperative anesthesia management of the burn patient. Surg Clin North Am 2014;94:851-61.
8. Hovgaard HL, Juhl-Olsen P. Suxamethonium-induced hyperkalemia: A short review of causes and recommendations for clinical applications. Crit Care Res Pract 2021;2021:6613118.
9. Palmer BF. Regulation of potassium homeostasis. Clin J Am Soc Nephrol 2015;10:1050-60.
10. Stone WA, Beach TP, Hamelberg W. Succinylcholine-danger in the spinal cord injured patient. Anesthesiology 1970;32:168-9.
11. Tobey RE. Paraplegia succinylcholine and cardiac arrest. Anesthesiology 1970;32:359-64.
12. Mortada H, Altuawijri I, Alhumsi T. The use of a single-piece bone flap for cranial reshaping in anterior craniosynostosis patients: Clinical experience and a description of a novel technique. Maxillofac Plast Reconstr Surg 2022;44:2.
13. Kachaeva EV, Ushakov IB, Shenkman BS. [Activity of the skeletal muscle proteolytic systems during functional unloading]. Usp Fiziol Nauk 2012;43:3-20.
14. Andel H, Markstaller K. Rapid-sequence-Narkoseeinleitung und Intubation – das Timing-Prinzip [Rapid sequence induction and intubation-the timing principle]. Anaesthesist 2019;68:46-7.
15. Consensus Conference. Electroconvulsive therapy. JAMA 1958;254:2103-8.
16. Thomas ET. Circulatory collapse following succinylcholine: Report of a case. Anesthesia Analg 1969;48:333-7.
17. Marco LA, Randels PM. Succinylcholine drug interaction electroconvulsive therapy. Biol Psychiatry 1979;14:433-45.
18. Kisor DF, Schmith VD. Clinical pharmacokinetics of cisatracurium besilate. Clin Pharmacokinet 1999;36:27-40.
19. Bryson HM, Faulds D. Cisatracurium besilate. A review of its pharmacology and clinical potential in anaesthetic practice. Drugs 1997;53:848-66.
20. Belmont MR, Lien CA, Quessy S, Abou-Donia MM, Abalos A, Eppich L, *et al*. The clinical neuromuscular pharmacology of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. Anesthesiology 1995;82:1139-45.
21. Pinard AM, Donati F, Martineau R, Denault AY, Taillefer J, Carrier M. Magnesium potentiates neuromuscular blockade with cisatracurium during cardiac surgery. Can J Anaesth 2003;50:172-8.
22. Brull SJ, Meistelman C. Pharmacology of neuromuscular blocking drugs. In: Gropper MA, editor. Miller's Anesthesia. 9th ed. Philadelphia, PA: Elsevier; 2020. p. 2751-93.
23. Mirinejad M, Azarfarin R, Asl AA. Cisatracurium in cardiac surgery--continuous infusion vs. bolus administration. Middle East J Anaesthesiol 2007;19:563-72.
24. Dear GJ, Harrelson JC, Jones AE, Johnson TE, Pleasance S. Identification of urinary and biliary conjugated metabolites of the neuromuscular blocker 51W89 by liquid chromatography/mass spectrometry. Rapid Commun Mass Spectrom 1995;9:1457-64.
25. Welch RM, Brown A, Ravitch J, Dahl R. The *in vitro* degradation of cisatracurium, the R, cis-R'-isomer of atracurium, in human and rat plasma. Clin Pharmacol Ther 1995;58:132-42.
26. Weindlmayr-Goettel M, Kress HG, Hammerschmidt F, Nigrovic V. *In vitro* degradation of atracurium and cisatracurium at pH 7.4 and 37 degrees C depends on the composition of the incubating solutions. Br J Anaesth 1998;81:409-14.
27. Kisor DF, Schmith VD, Wargin WA, Lien CA, Ornstein E, Cook DR. Importance of the organ-independent elimination of cisatracurium. Anesth Analg 1996;83:1065-71.
28. Cooper R, Mirakhur RK, Clarke RSJ, Boules Z. Comparison of intubating condition after administration of ORG – 9426 (Rocuronium) and suxamethonium. Br J Anaesth 1992;69:269-73.
29. Labrada DA, Vanegas GD, Costa OG. Rocuronium versus succinylcholine in the obese patient treated with laparoscopic bariatric surgery. Rev Cubana Anestesiol Reanimación 2019;18:1-14.
30. Shahryari H, Alavi S M, Ferasat Kish R, Motamed N, Karimi M. Comparison of propofol effect with Ketamine for sedation induction in pediatric patients who underwent cardiol catheterization. Iran South Med J 2010;13:16-23.
31. Deepika K, Kenaan CA, Bikhazi GB, Martineau DB. Influence of the priming technique on pharmacodynamics and intubating conditions of cisatracurium. J Clin Anesth 1999;11:572-5.
32. Mak PH, Irwin MG. The effect of cisatracurium and rocuronium on cisatracurium precurarization and the priming principle. J Clin Anesth 2004;16:83-7.
33. Yusuf AH, Okeke CI, Merah NA, Olatosi JO, Desalu IS, Kushimo OT. Comparison of suxamethonium and priming with atracurium for rapid sequence orotracheal intubation in a Nigerian adult population. Niger Postgrad Med J 2006;13:313-8.