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Original Article

A comparison of propofol and etomidate for anesthesia induction in patients with diabetic autonomic neuropathy

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Abstract

Objective: Diabetic autonomic neuropathy (DAN) is closely related with higher perioperative hemodynamic abnormalities. We predicted that etomidate produces less hemodynamic abnormalities than propofol during anesthesia induction in DAN patients.

Methods: The study included 40 DAN patients that undergo elective abdominal surgery with American Society of Anesthesiology classifications 2 or 3. In Group E, etomidate 0.3 mg/kg was given for induction of anesthesia. In Group P, propofol 2.5 mg/kg was applied for induction of anesthesia. Each group was consisted of 20 patients. Diastolic (DAP), systolic (SAP), mean arterial pressure (MAP) and heart rate (HR) values were measured before anesthesia induction (T0). Following the anesthesia induction, same measurements were conducted every minute for 5 minutes (T1-T5). Before anesthesia induction, following five minutes of endotracheal intubation and the surgical incision, the levels of serum insulin, cortisol and adrenocorticotropic hormone (ACTH) were analyzed.

Results: Average HR measurements were not different among the groups., average HR considerably reduced at T1 compared with T0 in Group P. Average SAP at T2 was noticeably fewer in Group P. Average SAP considerably decreased at T2 in both groups (p0.001) when compared with T0 values. At T1, T2, T3, and T5 times, patients in Group P showed noticeably decreased average DAP values than those in Group E. T1 average DAP noticeably decreased only in Group P ($p<0.001$) when compared with T0 values. At T1, average MAP was noticeably decreased in Group P compared with Group E ($p=0.033$). MAP noticeably decreased at T1 in both groups compared with T0 measurements ($p\leq0.006$). Serum levels of ACTH, cortisol, and insulin were not noticeably distinguishable among groups at any measurement time point.

Conclusion: When compared to propofol, etomidate is associated with fewer hemodynamic disturbances during anesthesia induction in diabetic patients with DAN.

Keywords: Anesthesia induction, diabetic neuropathy, etomidate, propofol.

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INTRODUCTION

Diabetes mellitus (DM) is an endocrine disease that is characterized by hyperglycemia and is caused by defects in the secretion of insulin hormone from the pancreas, its effect at the target organ, or both. Diabetes mellitus (DM) is an endocrine disease that affects more than 300 million people worldwide. Diabetes mellitus can be broken down into several subtypes, the most common of which is type 2 diabetes, which accounts for 90–95 percent of all cases of DM. In the year 2030, it is anticipated that type 2 diabetes will affect 7079 per one hundred thousand people all over the world and will reach a frequency of 10.1%. The average age of patients diagnosed with type 2 diabetes is over 20 (1,2).

Endothelial cells are most susceptible to damage when patients with diabetes have hyperglycemia. It damages the retina as well as the glomeruli and the vasa nervorum of the nerves. Neuropathy is a condition that can affect both the peripheral and the autonomic nervous systems, and it is caused by nerve involvement. As a result of the involvement of the vagus nerve, which is the longest nerve in the autonomic nervous system, diabetic autonomic neuropathy can lead to findings relating to a variety of organ systems. In relation to the affected system, symptoms such as cardiovascular autonomic neuropathy, gastrointestinal autonomic neuropathy, genitourinary autonomic neuropathy, sudomotor and vasomotor changes, pupillary dysfunction, and metabolic disorders can be observed (3,4) Approximately 20% of diabetics will develop a condition known as cardiovascular autonomic neuropathy (CAN), which is one of the most common and serious complications of diabetes. This rate may increase to as high as 73% with longer duration of diabetes treatment and increased age. Postural hypotension, orthostatic tachycardia and bradycardia syndromes, intraoperative cardiovascular instability, and silent myocardial ischemia/infarction are some of the symptoms and signs of CAN in diabetic patients. Other symptoms and signs include resting tachycardia and exercise intolerance (3,5,6)

There is a correlation between the presence of these signs and symptoms in diabetic patients and an increase in the risk of complications related to anesthesia. By altering the hemodynamic responses to the induction of anesthesia and endotracheal intubation, the presence of CAN leads to hypotension during surgery, which in turn raises the risk of morbidity and mortality associated with the procedure (6,7). During the induction of anesthesia, the sedatives etomidate and propofol are utilized because of their rapid onset of action. By binding to and stimulating peripheral alpha-2B adrenergic receptors, etomidate is able to cause a constriction of the blood vessels in the periphery. During its application, it has a negligible impact on the patient's hemodynamics. Because of this, it is frequently chosen as the method of anesthesia induction for patients who have low cardiac function or who have suffered trauma and shock. The most significant adverse effect of etomidate is adrenal inhibition, which can be observed with as little as a single dose, despite the fact that it only causes minor alterations in hemodynamics. During the induction of anesthesia, propofol inhibits the activity of the sympathetic nervous system, disrupts the regulatory mechanisms of the baroreflex, and causes vasodilation in the peripheral vessels. This results in a drop in blood pressure. Etomidate, on the other hand, keeps the blood pressure from fluctuating by preventing the autonomic reflexes from being affected (8,9)

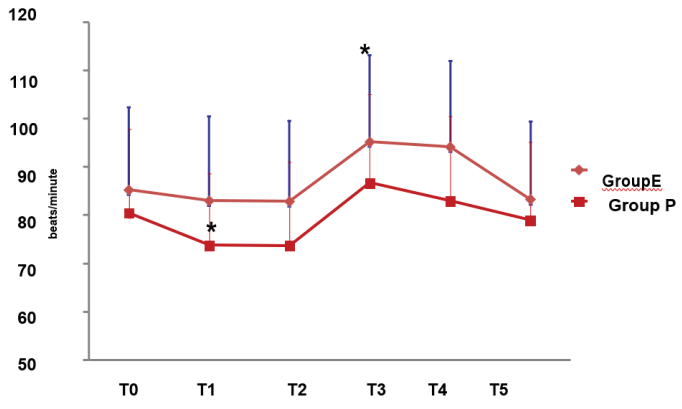

Figure 1. Average heart rate change according to the measurement time intervals of the groups

* Group P, when compared according to T0 values p=0.07

Group E, when compared according to T0 values p=0.012

In spite of the fact that there are a great deal of studies that contrast propofol and etomidate, there are not enough publications that focus on the use of these two medications in patients who have diabetic autonomic neuropathy. Comparing the hemodynamic and endocrine effects of propofol and etomidate during anesthesia induction in type 2 diabetic patients who also have autonomic neuropathy is the purpose of our study.

MATERIALS AND METHODS

Patient selection

The study was conducted with the approval of the Haseki Training and Research Hospital Ethics Committee. Forty patients, 17 of whom

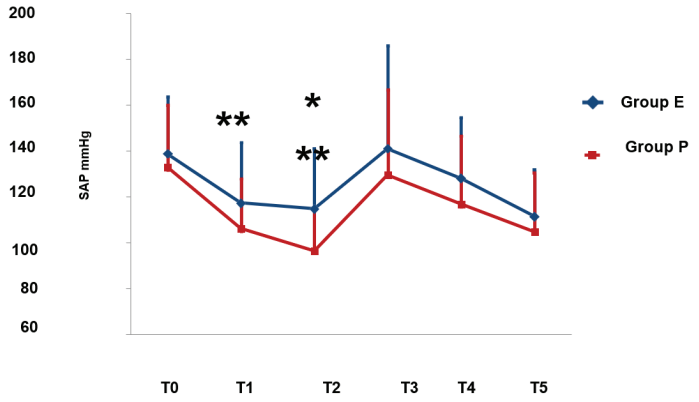

Figure 2. Systolic arterial (SAP) pressures of the groups at the measurement time intervals

*P=.016 Compared to Group P

** P=.014, P=.011 Compared with T0 values in both groups

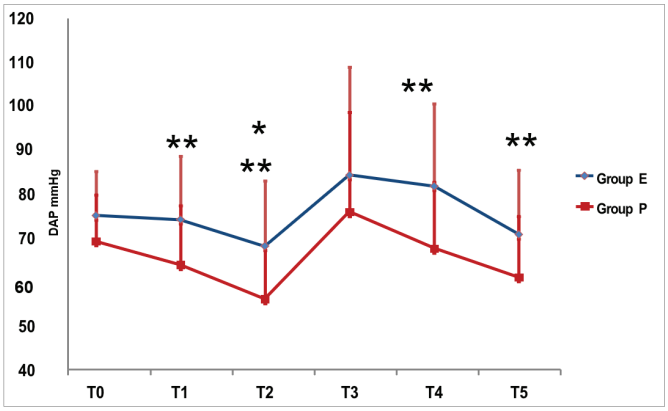

Figure 3. Mean diastolic arterial pressure (DAP) values of the groups at the measurement time intervals

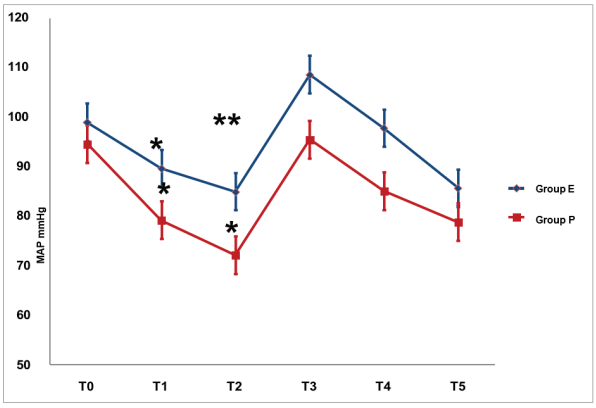

Figure 4. Mean arterial pressure values of the groups at the measurement time intervals

*P<.006 Compared with T0 in both groups

**P<.033 Compared to Group P

were male, over 35 years of age, in the ASA II-III group, who were diagnosed with type 2 diabetes mellitus and under control with oral antidiabetics were included after informing and receiving their informed consent. Cardiac autonomic neuropathy tests were performed in these patients and diabetic autonomic neuropathy was detected. Abdominal elective surgical intervention requiring endotracheal intubation under general anesthesia is planned for the patients.

Exclusion criteria

Those with type 1 diabetes and other causes of hyperglycemia, patients with diseases other than diabetes that may cause neuropathy, patients with hepatic and renal failure, patients with known allergies or contraindications to the drugs to be used, patients with any endocrine and metabolic disorders other than diabetes mellitus, patients who may experience difficulty in intubation were excluded.

Anesthesia

Oral antidiabetic drugs used by the patients were discontinued 1 day before the operation. On the morning of the operation, blood samples were taken from the patient for measurement of fasting blood glucose, ACTH, cortisol, insulin and arterial blood gas. Care was taken to make the cases the first case in the morning for the operation. Before induction of anesthesia, SpO_2 monitoring with pulse oximetry, ECG and noninvasive blood pressure monitoring were performed. After vascular access was established with a 22 gauce intravenous (i.v.) cannula patients were given midazolam 1-1.5 mg i.v. 3-5 minutes before induction of anesthesia. 0.9% NaCl infusion was started at a rate of 6-10 mL/kg/hour. Just before induction, systolic arterial pressure, diastolic arterial pressure, mean arterial pressure and heart rate values were measured and these values were recorded as control values. The patients were classified to two groups as Group P (Propofol) and Group E (Etomidate). After administering 1 µg/kg fentanyl and 1 mg/kg lidocaine HCl i.v. to all patients; 0.3 mg/kg etomidate was given to Group E and 2-2.5 mg/kg propofol was given to Group P within 20 seconds for anesthesia induction, and muscle relaxation was achieved with 0.6 mg/kg rocuronium. Mask ventilation was provided with 100% O_2 and endotracheal intubation was applied to the patients at the second minute. Anesthesia was maintained with 2% sevoflurane and 50% N_2O-O_2 inhalation. The maintenance of muscle relaxation was achieved by the administration of 0.06 mg/kg i.v rocuronium.

Table 1. Hypertension frequencies, HbA1c levels and demographic data of the groups (mean ±SD or number -%-)

	Group E (n=20)	Group P (n=20)	P
Age (years)	59.2 ± 11.9	55.7 ± 13.4	.406
Weight (kg)	79.8 ± 15.2	78.8 ± 10,6	.810
Height (cm)	165.2 ± 7.5	167.8 ± 6,7	.248
Female (%)	15 (75)	8 (40)	.057
HbA1c	7.5 ± 1.2	7.7 ± 1.6	.651
Hypertension(%)	**15 (75)**	**12 (60)**	**.250**

Measurements

Evaluation of diabetic autonomic neuropathy: The presence of autonomic neuropathy was evaluated by performing triple autonomic neuropathy tests the day before the operation (10).

30:15 R-R Ratio: ECG recording is taken while the patient is lying down. Recording continues when the patient is placed in a sitting position. Normally, the heart rate increases around the 15th beat and slows down around the 30th beat. The ratios of the R-R distances at the 30th and 15th beats are calculated. Values below 1.03 are considered as abnormal.

Arterial blood pressure response to sitting: Blood deeply 6 times per minute. The maximum pressure values are measured while the patient is lying down and 2 minutes after sitting. A drop in systolic blood pressure of more than 30mmHg is considered to be abnormal.

R-R interval variations for deep breathing: The patient breathes and minimum R-R intervals are measured during each respiratory cycle and converted to beats per minute. The average of these 6 measurements is taken. Less than 10 is considered to be abnormal.

Hemodynamic parameters:

Systolic (SAP), diastolic (DAP), mean (MAP) arterial pressure, heart rate (HR) were recorded before induction as control (T0) and every minute for 5 minutes after induction of anesthesia (T1-T5).

Hormone measurements: For the measurement of ACTH, cortisol, insulin levels, blood samples were collected before the operation (control), 5 minutes after intubation, and 5 minutes after the surgical incision. Samples were sent to the laboratory in cold storage.

Management of blood glucose during the operation

After taking blood samples for hormone measurements,1-1.5 ml/kg of 16 IU Crystallized insulin and 10 mEq KCl solution in 5% Dextrose was infused through a separate intravenous line. After measuring the blood glucose value preoperatively, capillary blood glucose values were measured every 30 minutes from the other side without fluid infusion. Insulin-dextrose infusion was adjusted to blood glucose value of 60-180 mg/dl.

Statistical Analysis

The obtained data were evaluated by entering the SPSS 10.0 ready-made statistics program. In the evaluation of the data, chi-square, Mann Whitney U test and Kruskal Wallis test were used in comparison of demographic data, hemodynamic parameters and hormone levels, and differences within the groups. $p<0.05$ was accepted as statistically significant.

RESULTS

In the study investigating the hemodynamic and endocrine effects of etomidate and propofol in diabetic cardiac autonomic neuropathy positive type 2 diabetic patients, no significant difference was found between the groups in terms of additional disease, demographic data, HbA1c and baseline hemodynamic measurements (Table 1, Figure 1, Figure 2, Figure 3, Figure 4).

There was no significant difference between the groups in terms of biochemical parameters and duration of diabetes.

Table 2. Mean ACTH, cortisol, insulin levels (mean ±SD) of the groups.

	Group E (n=20)	Group P (n=20)	P
ACTH (pg/ml)			
T0	22.1 ± 16	26.1 ± 19.3	0.435
T1	28.6 ± 22.9	26 ± 22	0.901
T2	44 ± 35.8	28.9 ± 19.9	0.301
Cortisol (mg/dl)			
T0	16.3 ± 5.6	18.1 ± 9.4	0.888
T1	17.1 ± 5.5	16.9 ± 9.6	0.414
T2	15.3 ± 5.3	15.7 ± 9.7	0.495
Insulin (IU/ml)			
T0	9.2 ± 7.9	10.4 ± 7.5	0.616
T1	24.5 ± 5.4	9.7 ± 8.7	0.531
T2	21.5 ± 4.1	6.4 ± 4.3	0.813

Abbreviations: *T0: Baseline value. Before anesthesia induction, T1: 5 minutes after intubation T2: 5 minutes after surgical incision*

There was no statistically significant difference between the groups in terms of HR values at all measurement times (p>0.05). Mean HR was significantly reduced in T1 compared with baseline T0 in the propofol group (Figure 1). T3 period HR was significantly higher in the etomidate group compared to the T0 control value (p=0.012). No significant difference was found in the propofol group. HR was slightly higher in the etomidate group when all times were taken into account without statistical significance.

T1 and T2 SAP values were determined to be noticeably lower in both etomidate and propofol groups (particularly in the propofol group), compared to T0 values (p=0.014, p=0.011, accordingly). The mean SAP value at T2 of the propofol group was significantly lower than the etomidate group (p=0.016). SAP values were slightly higher in the etomidate group, with no significant difference between all times (Figure 2).

The mean DAP values of the propofol group at T1, T2, T4 and T5 were significantly lower than the etomidate group (p=0.027, p=0.009, p=0.012, p=0.037, respectively). Considering the DAP values at T0 and T3, there was no difference between the groups (p>0.05). While there was no significant change in DAP value in the etomidate group at any time interval (p>0.05) when compared to the initial control values, T2 DAP values in the propofol group were significantly decreased compared to baseline T0 values (p=0.012). DAP values were slightly higher than propofol in all periods in the etomidate group without statistical significance (Figure 3).

MAP in the T2, the etomidate group was noticeably higher than the propofol group (p=0.033). Regarding MAP levels at other time points, there was no statistically significant difference between the groups (p>0.05). MAP values at T1 and T2 periods were significantly lower in both groups compared to baseline control values. MAP value of etomidate group at all-time intervals was insignificantly higher than that of propofol group (Figure 4).

In this research, there was no noticeable difference discovered between the two groups regarding serum ACTH, cortisol and insulin levels at all-time (p>0.05) (Table 2). There was no statistically significant difference in blood glucose follow-up values between the groups during the operation (p>0.05).

DISCUSSION

In this study, the hemodynamic and endocrine effects of type 2 diabetic patients with cardiac autonomic neuropathy during anesthesia induction with etomidate and propofol were compared. In both groups, systolic arterial pressures in the T1 and T2 time intervals were significantly reduced compared to the pre-induction T0

value. The reduction was more pronounced in the propofol group. When the groups were compared, the SAP value at T2 was significantly lower in the propofol group. In parallel with the change in systolic arterial pressure, MAP value has decreased at T1 and T2 in both groups and remained lower in propofol group than etomidate group at the T2 time interval. The significant heart rate reduction seen at the T1 period compared to the T0 baseline value in the propofol group was not observed in the etomidate group. This may suggest that etomidate provides a more stable course in patients with impaired sympathetic response to anesthesia induction due to diabetic cardiac autonomic neuropathy. Considering the measurement times in the study, T3 measurement time corresponds to three minutes after baseline, that is, one minute after endotracheal intubation. In this period, the increase in HR in the etomidate group may be due to the fact that etomidate did not change the normal hemodynamic response to endotracheal intubation. On the other hand, the lack of increase in HR in the propofol group may be due to impaired hemodynamic response in patients with cardiac autonomic neuropathy. These results are similar with the results of Ebert (9) et al.'s study evaluating the sympathetic response induced by anesthesia induction. Through this way, since sympathetic tone and baroreflex mechanism are impaired due to propofol induction, tachycardia response did not occur in response to the decrease in SAP in T1 and T2 periods. In contrast, HR was decreased in the propofol group during the T1 period recorded immediately after induction. Although sympathetic tone and baroreflex mechanisms appear to be unaffected by etomidate in healthy volunteers, the decrease in SAP observed in the etomidate group may be due to impaired autonomic reflexes in patients with cardiac autonomic neuropathy. However, etomidate causes a more stable HR value in the periods immediately after induction and provides an increased heart rate response after intubation. While there was no significant change in the DAP value in the etomidate group at any time interval compared to the control value, decrease in T2 in the propofol group and a lower DAP value compared to etomidate at T1, T2, T4 and T5 periods suggests that the sympathetic blockade and vasodilation effect of propofol is potentiated in patients with diabetic cardiac autonomic neuropathy. In addition, the vasodilation and hypotension inhibitory effect of etomidate with its sympathetic alpha-2B stimulating effect suggests that it is also protective in this patient group. Although there is no study in the literature comparing the effects of etomidate and propofol in diabetic patients with autonomic neuropathy, Keyl et al., investigating the effects of diabetic autonomic neuropathy during anesthesia induction in coronary artery surgery, reported that there was no hemodynamic change in anesthesia induction between patients with positive cardiac autonomic neuropathy tests and those without cardiac autonomic neuropathy (11). In this study, in which anesthesia induction was provided by etomidate, the absence of suppressive effect of etomidate on sympathetic tone and baroreflex mechanisms may have provided hemodynamic stability. These findings are consistent with the more stable hemodynamic status provided by etomidate in our study. Propofol caused a greater decrease in arterial pressures, especially in DAP value.

Baradari et al. investigated the effects of a mixture of etomidate, propofol and ketamine on the induction of anesthesia in patients who will undergo coronary artery bypass surgery with an ejection fraction of less than 40% and found that etomidate induction provided better hemodynamic conditions in this patient group with insufficient left heart ejection fraction (12). These findings are similar to the effects of etomidate in the induction of anesthesia in patients with autonomic neuropathy in whom both systolic and diastolic functions were impaired.

In the study of Hannam et al., comparing the hemodynamic effects of etomidate and propofol in the induction of patients undergoing elective coronary artery, heart valve disease, or a combination of both, and thoracic aorta surgery, changes in MAP values and vasopressor requirement were compared with baseline values before induction and 10 minutes after induction (13). Although more vasopressors were used in the propofol group, there was a 34% greater reduction in MAP value. The adrenal suppressive effect of even a single use of etomidate at induction doses is known. Kaushal et al. compared the hemodynamic and endocrine effects of etomidate and propofol in 60 patients undergoing elective cardiac surgery and determined that cortisol levels decreased significantly during the bypass after etomidate induction and during the weaning period from cardiopulmonary bypass (14). It was stated that this decrease in cortisol levels returns to normal at the end of 24 hours and did not have any negative effect on hemodynamics of patients. In our study, etomidate had no effect on ACTH, cortisol and insulin levels at induction doses, and it induced a stable hemodynamic response in patients with positive cardiac autonomic neuropathy.

CONCLUSION

Etomidate causes less hemodynamic changes when compared with propofol in the induction of anesthesia in type 2 diabetic patients with autonomic neuropathy. In addition, since the use of induction doses does not cause any change in cortisol, insulin and ACTH levels in the short term, it suggests that it can be safely preferred for

induction of anesthesia in type 2 diabetic patients with autonomic neuropathy.

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Ethical approval: The study was conducted with the the conditions recommended by the Helsinki Declaration and approval of the Haseki Training and Research Hospital Ethics Committee.

Peer review: Externally peer-reviewed.

Author contributions: Design of the study; RSK, SU - Supervision; RSK, SU - Data collection &/or processing; RSK, SU - Performed data analysis; RSK, SU - Literature search; RSK - Written by; RSK, SU - Critical review; RSK.

References

1. El Sayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023. Diabetes Care. 2023 Jan 1;46(1):S19–40.
2. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Kaabi J, et al. Epidemiology of Type 2 diabetes - Global burden of disease and forecasted trends. J Epidemiol Glob Health. 2020;10(1).
3. Williams S, Raheim SA, Khan MI, Rubab U, Kanagala P, Zhao SS, et al. Cardiac Autonomic Neuropathy in Type 1 and 2 Diabetes: Epidemiology, Pathophysiology, and Management. Vol. 44, Clinical Therapeutics. Elsevier Inc.; 2022. p. 1394–416.
4. Aso Y. Updates in diabetic neuropathy: A call for new diagnostic and treatment approaches. J Diabetes Investig. 2022;13(3).
5. Şahin M. Diyabetik otonom nöropatide güncel tanı ve tedavi yaklaşımları. Abant Tıp Dergisi. 2017;6(3):129–33.
6. Spallone V. Update on the impact, diagnosis and management of cardiovascular autonomic neuropathy in diabetes: What is defined, what is new, and what is unmet. Vol. 43, Diabetes and Metabolism Journal. 2019.
7. Oakley I, Emond L. Diabetic cardiac autonomic neuropathy and anesthetic management: Review of the literature. Vol. 79, AANA Journal. 2011.
8. Creagh O, Torres H, Rodríguez N, Gatica SR. Alpha-2B adrenergic receptor mediated hemodynamic profile of etomidate. Vol. 29, Puerto Rico Health Sciences Journal. 2010.
9. Ebert TJ, Muzi M, Berens R, Goff D, Kampine JP. Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. Anesthesiology. 1992;76(5).
10. Argente-Pla M, Pérez-Lázaro A, Martinez-Millana A, del Olmo-García MI, Espí-Reig J, Beneyto-Castello I, et al. Simultaneous Pancreas Kidney Transplantation Improves Cardiovascular Autonomic Neuropathy with Improved Valsalva Ratio as the Most Precocious Test. J Diabetes Res. 2020;2020.
11. Keyl C, Lemberger P, Palitzsch KD, Hochmuth K, Liebold A, Hobbhahn J. Cardiovascular autonomic dysfunction and hemodynamic response to anesthetic induction in patients with coronary artery disease and diabetes mellitus. Anesth Analg. 1999;88(5).
12. Baradari AG, Alipour A, Habibi MR, Rashidaei S, Zeydi AE. A randomized clinical trial comparing hemodynamic responses to ketamine-propofol combination (ketofol) versus etomidate during anesthesia induction in patients with left ventricular dysfunction undergoing coronary artery bypass graft surgery. Archives of Medical Science. 2017;13(5).
13. Hannam JA, Mitchell SJ, Cumin D, Frampton C, Merry AF, Moore MR, et al. Haemodynamic profiles of etomidate vs propofol for induction of anaesthesia: a randomised controlled trial in patients undergoing cardiac surgery. Br J Anaesth. 2019;122(2).
14. Kaushal RP, Vatal A, Pathak R. Effect of etomidate and propofol induction on hemodynamic and endocrine response in patients undergoing coronary artery bypass grafting/mitral valve and aortic valve replacement surgery on cardiopulmonary bypass. Ann Card Anaesth. 2015;18(2).