ORIGINAL RESEARCH

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Changes of autonomic tonus of the heart during induction of general anesthesia with two intravenous anaesthetics

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Abstract

Background: Induction of general anesthesia with midazolam or thiopental is often associated with cardiovascular changes.
Material and methods: The study group involved 94 patients. The analysis of heart rate variability and the changes in cardiac vegetative tonus was performed after premedication with fentanyl solution and after induction of general anesthesia with midazolam combined with fentanyl (midazolam group) or thiopental combined with fentanyl (thiopental group).
Results: After administration of fentanyl in doses of 1.0 mkg/kg for premedication there were no significant changes of heart rate variability and vegetative heart tonus in both groups. Administration of midazolam 0.2-0.3 mg/kg combined with fentanyl 1.0 mkg/kg for induction of general anesthesia leads to a significant reduction of heart rate variability. The LFun (marker of sympathetic heart tonus) reduced by 24.2% (69.1 (95%CI 65.9-72.3) vs 52.4 (95%CI 42.9-70.0) (p=0,02), meantime the HFun (marker of parasympathetic cardiac tonus) enhanced by 34,9% (30,9 (95%CI 27.6-34.1) vs 47.5(95% CI 30.4-57.4) (p=0.01). Administration of thiopental 6.0-7.0 mg/kg combined with fentanyl 1.0 mkg/kg for induction of general anesthesia leads to a significant reduction of heart rate variability.
Conclusions: Administration of fentanyl solution in doses 1.0 mkg/kg for premedication is not associated with significant changes of vegetative tonus of the heart. Administration of midazolam in combination with fentanyl for induction of general anesthesia leads to significant decrease of heart rate variability and enhanced parasympathetic cardiac tonus. Induction of general anesthesia with thiopental and fentanyl leads to enhanced sympathetic tonus of the heart and reduced parasympathetic tonus of the heart.
Key words: heart rate variability, sympathetic heart tonus, parasympathetic heart tonus.

Introduction

Midazolam is a hypnotic agent used for sedation as well as for induction of general anesthesia. Frequently, its intravenous administration is associated with blood pressure and heart rate changes. Midazolam acts via gamma-aminobutyric acid (GABA) receptors which have an important role in regulation of vegetative nervous system [1, 2].

Thiopental is an ultra-short acting derivative of barbiturates. Large clinical application of the drug has been accompanied by an enormous increase in the knowledge of the pharmacology, in particular the effects on GABA receptor and GABA-induced effects on nerve cell membranes. Despite the development of new agents for induction o general anesthesia, thiopental still has a firm place in clinical applications. Currently it is mainly used in obstetrics for induction of cesarean sections under general anesthesia. Also, this is preferred agent of induction in neurosurgery [3-6].

Fentanyl is an opioid used in combination with other hypnotic agents for induction of general anesthesia [7].

The sympathetic and parasympathetic influences on the sinus node in the heart are manifested by cyclic changes of the RR interval on the ECG, a phenomenon known as heart rate variability (HRV). HRV is a widely used method to assess changes in vegetative tonus of the heart in different medical fields [8, 9, 10]. Some recent studies have demonstrated the efficacy of HRV analysis for risk assessment of hemodynamic instability during induction of anesthesia in abdominal surgery [11, 12].

Induction of general anesthesia with thiopental or midazolam is associated with changes in blood pressure and heart rhythm. These changes can be attributed to direct effects of the drugs on the heart, changes in arterial blood pressure and activation of baroreceptor mechanisms, peripheral vasodilation (preferential mechanism for barbiturates like thiopental). In the literature there are several studies which analysed the effects of midazolam [1, 13-19] and the effects of thiopental [20, 21, 22] on sympathetic-parasympathetic balance of the heart. There is not a single comparative study regarding changes in autonomic tonus of the heart during induction of anesthesia with midazolam or thiopental.

This study tested the hypothesis that induction of general anesthesia with thiopental or midazolam is associated with changes in autonomic tonus of the heart. The study hypothesis started from the clinical observation that the combination of midazolam and fentanyl for induction of anesthesia frequently is associated with development of arterial hypotension and sinus bradycardia, while induction with thiopental and fentanyl more often led to arterial hypotension and sinus tachycardia.

Material and methods

This is a prospective randomized study to evaluate the changes of vegetative heart tonus after induction of general anesthesia with two different anesthetic agents: midazolam and thiopental, both of them combined with fentanyl. The protocol of study was approved by the Ethic Committee of the Nicolae Testemitsanu State University of Medicine and Pharmacy, Chișinău.

The study groups involved ASA physical status I-II patients scheduled for elective surgical procedures aged under 60 years (to exclude age-related changes of HRV). We obtained an informed consent from all participants in the study. Patients with diseases that could interfere with vegetative heart tonus (endocrine, neurological, cardiovascular diseases) were excluded from the study. Another exclusion criterion was the presence of more than 20% of artifacts on ECG trace. Another compulsory criterion was the presence of sinus rhythm on ECG in patients enrolled in the study group (fig. 1).

For registration of continuous ECG to provide analysis of HRV in order to find the change of autonomic tonus of

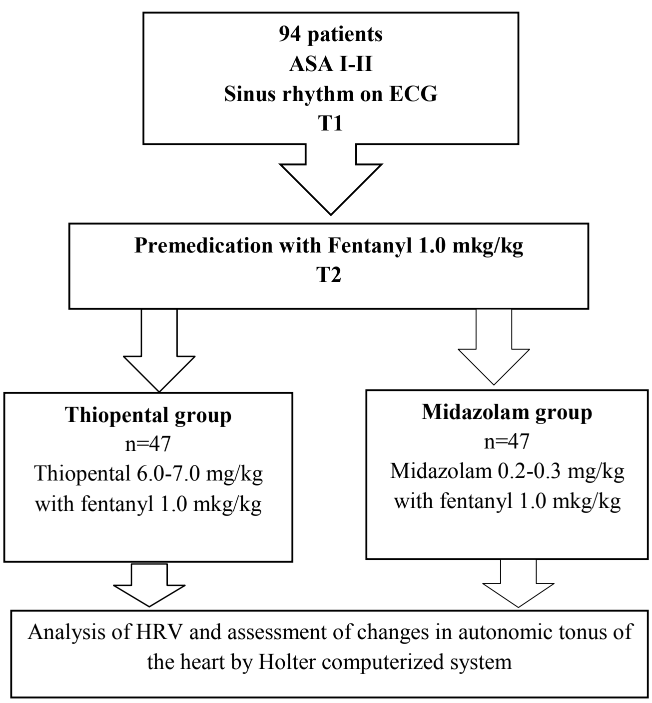

Fig. 1. Flowchart of the study.

the heart was used a Holter device (Holter TLC 5000, USA). We attached 10 electrodes on the chest and abdomen of the patients and connected them to Holter monitor. Continuous ECG registration was performed within 25-30 minutes after admission of patients to the surgical room. HRV parameters were analyzed at rest (T1), after premedication with fentanyl 1.0 mkg/kg (T2) and after induction of general anesthesia with midazolam 0.2-0.3 mg/kg with fentanyl 1.0 mkg/kg (midazolam group) and thiopental 6.0-7.0 mg/kg with fentanyl 1.0 mkg/kg (thiopental group) (fig. 1). After administration of midazolam or thiopental and development of bradypnea or apnea, the mask ventilation was initiated in order to ensure a frequency of ventilation of 14-16/min and a tidal volume 7.0-8.0 ml/kg, an important requirement for correct registration and analysis of HRV. During induction of general anesthesia, oxygen was delivered to ensure a SpO_2 above 95%.

HRV parameters and changes in sympathetic and parasympathetic vegetative heart tonus were analyzed by Holter computerized system. Parameters of HRV and their significance were interpreted according to the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [13]. Total Power (TP) of HRV represents all vegetative influences on the heart (sympathetic, parasympathetic, influences from chemoreceptors and baroreceptors)(physiological ranges – 3466.0±1018.0 ms^2); spectral power of normalized low frequency power (LFun) (physiological ranges – 54.0±4.0) represents sympathetic and baroreceptor influences on the heart; spectral power of normalized high frequency power (HFun) (physiological ranges – 29.0±3.0) represents parasympathetic influences on the heart; LFun/HFun ratio (physiological ranges – 1.5-2.0) – represents sympathetic-parasympathetic balance of the heart [8, 10].

Statistical analysis of the results was done with the statistical program GraphPad Prism 8 (GraphPad Software, San Diego, California, SUA). For analysis of HRV changes within one group were used paired t-test and repeated measures ANOVA (for values with parametric distribution) and Wilcoxon and Friedman tests (for values with non-parametric distribution). For statistical analyses between groups (thiopental group vs. midazolam group) were used unpaired t-test (for values with parametric distribution) and Mann-Whitney and Kruskal–Wallis tests (for values with non-parametric distribution). Results are presented in form of average and 95% confidence interval (for parametric data) and median with interquartile range (IQR - for non-parametric data). Value of $p<0.05$ was considered statistically significant. The number of patients involved in the study group was determined in order to ensure a study power of 80%.

Results

A total of 94 patients comprising 43 men and 51 women were studied. None of the patients was excluded from the study. Demographic data are shown in Table 1. There were no significant differences between groups in terms of demographic data. The distribution of ASA physical status classification and operative procedures was also comparable in two groups (tab. 1 and 2).

Table 1

Demographic data

Parameters	Group		p
	Midazolam	Thiopental	
Age in years (mean±SD)	38.0±12.0	35.4±11.2	0.86
BMI in kg/m² (mean±SD)	24.5±3.3	23.9±4.1	0.19
Male/Female	20/27	23/24	NS
ASA I/II	21/26	19/28	NS

SD=Standard deviation, BMI = body mass index; NS=Not significant, ASA=American Society of Anesthesiologists

The baseline values of HRV parameters (TP, LFun, HFun and LFun/HFun) for both groups are presented in the table 3. There was no statistically significant difference between groups. It can be observed that the baseline value of LFun/HFun was 3.1 (95%CI 2.4-3.8) in midazolam group and 2.7 (95% CI 2.1-3.3) in thiopental group, indicating enhanced cardiac sympathetic tonus in the patients of both study groups.

Table 2

Distribution of operative procedures in the study groups

Operative procedures	Midazolam group (n=47)	Thiopental group (n=47)
Laparoscopic cholecystectomy	18	18
Mandible osteosynthesis	9	9
Discectomy	12	8
Rhinoplasty	5	4
Sinusotomy	3	2
Others	-	6

After administration of fentanyl 1.0 mkg/kg for premedication the parameters of HRV didn't change significantly when comparing to baseline values. There were no attested significant differences between groups as well (table 3). The major changes in HRV parameters were attested after administration of midazolam 0.2-0.3 mg/kg or thiopental 6.0-7.0 mg/kg for induction of general anesthesia.

After intravenous administration of midazolam the spectral power of TP decreased by 81.9% (149.3 ms^2 (IQR 52.0-320.0) vs 829.1 ms^2 (IQR 438.5-2395.0), (p=0.001). After intravenous administration of thiopental the spectral power of TP decreased by 88.5% (100.4 ms^2 (IQR 54.7-188.8) vs 869.5 ms^2 (IQR 512.2-1633.0) (p<0.0001) (fig. 2).

Table 3

HRV parameters in both study groups

HRV parameters		Baseline (T1)	After premedicatio (T2)	After induction (T3)	p
TP (ms^2) *	Midazolam group	924.2* (404.2-1913.0)	829.1* (438.5-2395.0)	149.3* (52.0-320.0)	0.0001
	Thiopental group	889.5* (481.7-1585.0)	869.5* (512.2-1633.0)	100.4* (54.7- 188.8)	**<0.0001**
p		**0.68**	**0.9**	**0.014**	
LFun	Midazolam group	67.7 (62.9-72.5)	69.1 (65.9-72.3)	52.4 (42.9-70.0)	0.02
	Thiopental group	65.5 (60.8-70.1)	65.8 (61.9-69.6)	73.5 (68.4-78.6)	<0.001
p		**0.49**	**0.18**	**0.03**	
HFun	Midazolam group	27.4 (21.4-37.0)	30.9 (27.6-34.1)	47.5 (30.4-57.4)	**0.01**
	Thiopental group	34.5 (29.8-39.2)	34.2 (30.4-38.1)	24.5 (20.3-28.7)	**<0.001**
p		**0.5**	**0.18**	**0.01**	
LFun/HFun	Midazolam group	3.1 (2.4-3.8)	2.8 (2.2-3.4)	1.1 (0.6-1.8)	**0.03**
	Thiopental group	2.7 (2.1-3.3)	2.4 (2.0-2.8)	4.4 (3.5-5.2)	**<0.001**
p		**0.33**	**0.26**	**0.01**	

Note. Statistical analysis was performed with repeated measures ANOVA and Friedman test* (for analysis within the group) and unpaired t-test and Mann-Whitney test* (for analysis between groups). Values are presented as average and 95% confidence interval for values with parametric distribution and median with interquartile range for parameters with non-parametric distribution*.

It is worth mentioning that induction of general anesthesia with thiopental and fentanyl depresses HRV more than induction with midazolam and fentanyl (p=0.014).

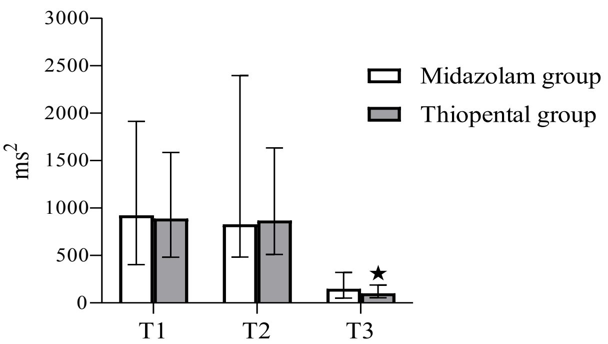

Fig. 2. Changes of spectral power of TP of HRV in both study groups.
(*p<0.05) Values are represented as median with intercuartile range (error bars.)

There were attested significant changes in the spectral power of LFun and HFun after administration of thiopental or midazolam. These changes are different in each group, in such a way emphasizing the different effects of thiopental and midazolam on the cardiac vegetative tonus.

In the midazolam group in T3, LFun decreased by 24.2% (52.4 (95%CI 42.9-70.0) vs 69.1 (95%CI 65.9-72.3), (p=0.02), demonstrating the sympatholytic effect of the drug, while in thiopental group LFun enhanced by 10.5% (73.5 (95%CI 68.4-78.6) vs 65.8 (95%CI 61.9-69.6) (p<0.001), proving sympathomimetic effect of anesthetic agent (fig. 3).

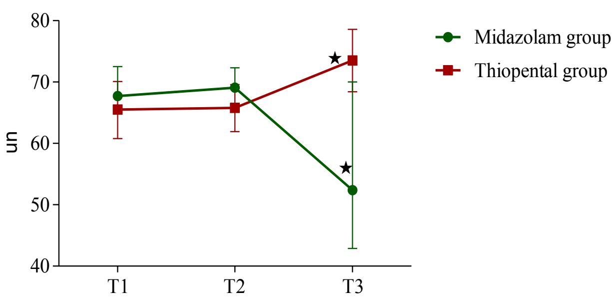

Fig. 3. Changes of spectral power of LFun in both study groups.
(*p<0.05) Error bars represent 95% confidence interval.

Spectral power of HFun (marker of parasympathetic heart tonus) also changed significantly after administration of thiopental or midazolam. Changes of spectral power of HFun after administration of midazolam proved the vagotonic effect of the drug since power of HFun increased by 34.9% (47.5 (95%CI 30.4-57.4) vs. 30.9 (95%CI 27.6-34.1) (p=0.01). In the thiopental group spectral power of HFun has reduced by 28.4% (34.2 (95%CI 30.4-38.1) vs. 24.5 (95%CI 20.3-28.7)(p=0.001). Reduction in power of HFun demonstrated the vagolytic effect of thiopental when given in doses for induction of general anesthesia and combined with fentanyl (fig. 4).

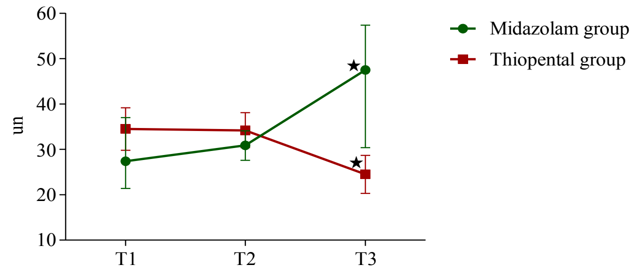

Fig. 4. Changes of spectral power of HFun in both study groups.
(*p<0.05) Error bars represent 95% confidence interval.

Changes of LFun and HFun in both groups lead to changes in LFun/HFun ratio.

After induction of general anesthesia with midazolam and fentanyl the LFun/HFun ratio decreased by 60.7% (1.1 (95%CI 0.6-1.8) vs. 2.8 (95%CI 2.2-3.4)(p=0.03). The value of LFun/HFun ratio after induction was 1.1 which indicated enhanced cardiac parasympathetic tonus in the patients of the study group. In the thiopental group the average LFun/HFun in T3 was 4.4, signaling the predominance of sympathetic tonus of the heart, showing an enhancement by 45.5% (2.4 (95%CI 2.0-2.8) vs. 4.4 (95%CI9 3.5-5.2) (p<0.001) (fig. 5).

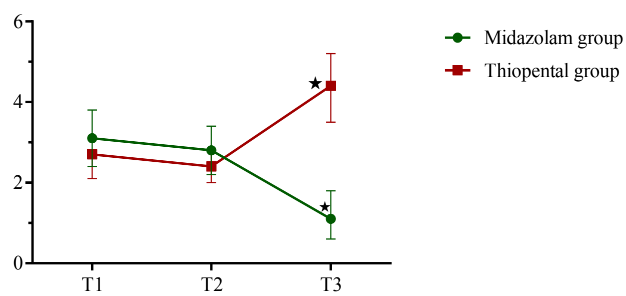

Fig. 5. Changes of LFun/HFun ratio in both study groups.
(*p<0.05) Error bars represent 95% confidence interval.

Discussion

The sinus node of the heart is under permanent control of vegetative nervous system thus controlling the heart rhythm and performing adaptation to different physiological or pathological factors. The changes in heart rhythm and subsequently changes in HRV are triggered by sympathetic and parasympathetic input on the sinus node. HRV is a frequent tool used in medical field for analysis of changes in sympathetic and parasympathetic influences on the heart. Nowadays to analyze HRV is an easy goal since modern Holter devices are equipped with computerized system for analysis of HRV and can appreciate the changes in heart vegetative tonus. It was generally accepted and proved in many clinical researches, that the LFun/HFun ratio represents the sympathetic-parasympathetic balance of the heart, the LFun represents the sympathetic and baroreceptors influences on the heart and the HFun represents the parasympathetic tonus of the heart [9, 10, 13].

Several clinical studies used analysis of HRV to find the effect of midazolam on vegetative regulation of the heart. The fact should be mentioned that in most of these studies midazolam was administered intravenously for sedation [1, 14, 15]. So, it is difficult to compare their results with the results of this study, since the midazolam dose was higher (0.2-0.3 mg/kg) and it was administered in combination with fentanyl (1.0 mkg/kg).

In a recent study Nishiyama T. (2018), demonstrated that administration of midazolam 0.06 mg/kg in combination with 0.5 mg of atropine reduced sympathetic tonus. The final conclusion of the study was that midazolam, but not hydroxyzine premedication, inhibited sympathetic activation at induction of anesthesia with midazolam and thiopental [1].

In another study performed by Tsugayasu R. et al. [14], sedation with midazolam 0.01 mg/kg decreased cardiac sympathetic tonus without significant effect on cardiac parasympathetic tonus. Smith A. et al. showed that premedication with midazolam 2.5 mg in combination with differential doses of fentanyl (50 mkg, 75 mkg, 100 mkg and 150 mkg) didn't change significantly the cardiac vegetative tonus. The final conclusion of this clinical study was that midazolam for sedation in combination with fentanyl didn't change the autonomic balance of the heart and the enhanced cardiac sympathetic tonus in the patients from the study group mostly was triggered by changes in respiratory pattern [15].

Contrary to this, in another clinical research by Dogan I. et al. was proved that sedation with midazolam 0.05 mg/kg for transesophageal echocardiography significantly reduced cardiac sympathetic tonus and significantly increased parasympathetic tonus [16]. The results of this study are similar to our results, even if the dose of midazolam was lower. In our study value of LFun/HFun after induction of general anesthesia with midazolam and fentanyl decreased to 1.1 thus signaling enhanced cardiac parasympathetic tonus. This decrease could be attributed to the effects of midazolam, as premedication with fentanyl didn't significantly change LFun/HFun ratio. Benzodiazepines can influence autonomic neurocardiac regulation, probably through their interaction with the GABAA receptor complex in the brain [2].

Hidaka S. et al. in a prospective clinical research, involving forty ASA physical status I and II patients scheduled for knee surgery investigated the effect of propofol and midazolam on cardiac autonomic nervous system activity during combined spinal-epidural anesthesia [17]. In this clinical study, propofol was more potent than midazolam in causing sympatholytic effect during combined spinal and epidural anesthesia. Our research proved the same sympatholytic effect of midazolam when combined with fentanyl and given in doses for induction of general anesthesia.

In a clinical study involving thirty dental patients, Win N. et al. proved dominant sympathetic effect of midazolam [18]. In this clinical research, midazolam was associated with an increase in LF/HF ratio (2.3±1.1 versus 3.7±1.8). It should be emphasized that the dose of midazolam in this study was 0.075 mg/kg, much lower than in our study.

In a controlled, randomized, double-blinded study by Sherif S. et al. aiming to investigate the effects of intravenous midazolam on HRV, patients received midazolam 0.05 mg/kg. In this clinical research, midazolam administered in sedative doses induced a significant decrease in TP and HF power, reflecting decreased parasympathetic activity. There was a decrease in LF power that did not reach statistical significance [19].

There are several studies which analyzed the effects of thiopental on autonomic tonus of the heart by analysis of HRV according to recommendations of Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [13]. Tsuchiya S. et al. in a clinical study involving 17 patients scheduled for minor surgical interventions proved the fact that thiopental given in small doses for sedation, significantly reduced parasympathetic tonus of the heart without visible influences on sympathetic tonus of the heart [20]. Another remark of the study was that effect of thiopental on vegetative balance of the heart is in direct relation with the level of sedation. In our study induction with thiopental significantly enhanced sympathetic tonus of the heart and significantly reduced parasympathetic tonus of the heart, but the doses of the drug were higher. In another clinical research by Omerbegovic M. et al. [21] was compared the effect of propofol and thiopental on heart autonomic balance. The study group comprised only patients scheduled for surgery with ASA I-II risk. In this study the effect of propofol on HRV didn't differ significantly from the effect of thiopental, as induction in both groups of study leads to mark reduction of TP of HRV, LFun and HF. So, in this study was confirmed the sympatholytic and vagolytic effect of thiopental. Their results are different from ours, as in our study induction with thiopental and fentanyl reduced significantly HRV and HFun, thiopental having a vagolytic effect. The spectral power of LFun after administration of thiopental enhanced significantly, proving a sympathomimetic effect of the drug.

In a study conducted by Riznyk L. et al. [22], aiming to compare the effects of thiopental and propofol on heart rate variability during fentanyl-based induction of general anesthesia, after administration of fentanyl 3.0 mkg/kg there was a significant reduction in spectral power of LFun, proving the sympatholytic effect of opioid. In our study after premedication with 1.0 mkg/kg fentanyl were not attested significant changes in spectral power of LFun, HFun and LFun/HFun ratio. This may be explained by a lower dose of the drug which we used for premedication. After administration of thiopental in the study by Riznyk L. at al. as well as in this study, was proved the sympathomimetic effect (enhanced power of LFun and LFun/HFun ratio) and vagolytic effect (reduced power of HFun) of thiopental.

This clinical research of HRV analysis used to find changes in sympathetic-parasympathetic tonus of the heart proved its clinical applicability. By analysis of changes in spectral power of TP, LFun, HFun and LFun/HFun ratio was demonstrated the sympatholytic and vagotonic effect of midazolam and sympathomimetic and vagolytic effect of thiopental. This can be of huge clinical significance when choosing the drugs for induction of general anesthesia in patients with cardiovascular disorders or other diseases which interfere with autonomic regulation of the heart.

Conclusions

1. Induction of general anesthesia with thiopental and fentanyl depresses HRV more than induction with midazolam and fentanyl.

2. Administration of midazolam combined with fentanyl for induction leads to enhanced parasympathetic tonus of the heart (vagotonic effect) and reduces sympathetic tonus of the heart (sympatholytic effect);

3. Administration of thiopental combined with fentanyl for induction leads to enhanced sympathetic tonus of the heart (sympathomimetic effect) and reduces parasympathetic tonus of the heart (vagolytic effect).

References

1. Nishiyama T. Effects of premedication on heart rate variability at induction of anaesthesia: comparison between midazolam and hydroxyzine. Turk J Anaesthesiol Reanim. 2018;46:229-232.
2. Maldifassi M, Baur R, Pierce D, Nourmahnad A, Stuart A, Sigel E. Novel positive allosteric modulators of GABA-A receptors with anesthetic activity. Sci Rep. 2016;6:25943.
3. Dumps C, Halbeck E, Bolkenius D. Drugs for intravenous induction of anesthesia: barbiturates. Anaesthesist. 2018;67(7):535-552.
4. Hino H, Matsuura T, Kihara Y, Tsujikawa S, Mori T, Nishikawa K. Comparison between hemodynamic effects of propofol and thiopental during general anesthesia induction with remifentanil infusion: a double-blind, age-stratified, randomized study. J Anesth. 2019 Jun 21. doi: 10.1007/s00540-019-02657-x. [Epub ahead of print].
5. Naseri M, Parham A, Moghimi A. The effect of sodium thiopental as a GABA mimetic drug in neonatal period on expression of GAD65 and GAD67 genes in hippocampus of newborn and adult male rats. Iran J Basic Med Sci. 2017;20:996-1001.
6. Aslan NA, Vural Ç, Yılmaz AA, Alanoğlu Z. Propofol versus thiopental for rapid-sequence induction in isolated systolic hypertensive patients: a factorial randomized double-blind clinical trial. Turk J Anaesthesiol Reanim. 2018;46(5):367-372.
7. Suzuki J, El-Haddad S. A review: Fentanyl and non-pharmaceutical fentanyls. Drug Alcohol Depend. 2017;171:107-116.
8. Anderson T. Heart rate variability: implications for perioperative anesthesia care. Curr Opin Anaesthesiol. 2017;30(6):691-697.
9. Pichot V, Roche F, Celle S, Barthélémy J, Chouchou F. HRV analysis: a free software for analyzing cardiac autonomic activity. Front Physiol. 2016;22;7:557.
10. Mazzeo A, La Monaca E, Di Leo R, Vita G, Santamaria L. Heart rate variability: a diagnostic and prognostic tool in anesthesia and intensive care. Acta Anaesthesiol Scand. 2011;55:797-811.
11. Padley J, Ben-Menachem E. Low pre-operative heart rate variability and complexity are associated with hypotension after anesthesia induction in major abdominal surgery. J Clin Monit Comput. 2018;32(2):245-252.
12. Reimer P, Máca J, Szturz P, Jor O, Kula R, Ševčík P, Burda M, Adamus M. Role of heart-rate variability in preoperative assessment of physiological reserves in patients undergoing major abdominal surgery. Ther Clin Risk Manag. 2017;13:1223-1231.
13. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation. 1996;93(5):1043-1065.
14. Tsugayasu R, Handa T, Kaneko Y, Ichinohe T. Midazolam more effectively suppresses sympathetic activations and reduces stress feelings during mental arithmetic task than propofol. J Oral Maxillofac Surg. 2010;68(3):590-596.
15. Smith A, Owen H, Reynolds K. Can short-term heart rate variability be used to monitor fentanyl-midazolam induced changes in ANS preceding respiratory depression? J Clin Monit Comput. 2015;29(3):393-405.
16. Dogan Y, Eren G, Tulubas E, Oduncu V, Sahin A, Ciftci S. The effect of sedation during transoesophageal echocardiography on heart rate variability: a comparison of hypnotic sedation with medical sedation. Kardiol Pol. 2016;74(6):591-597.
17. Hidaka S, Kawamoto M, Kurita S, Yuge O. Comparison of the effects of propofol and midazolam on the cardiovascular autonomic nervous system during combined spinal and epidural anesthesia. J Clin Anesth. 2005;17:36-43.
18. Win N, Fukayama H, Kohase H, Umino M. The different effects of intravenous propofol and midazolam sedation on hemodynamic and heart rate variability. Anesth Analg. 2005;101:97-102.
19. Sherif S, Nasr A. Utilizing heart rate variability: midazolam prevents the sympathovagal imbalance caused by fentanyl/propofol induction. Ain-Shams J Anesthesiol. 2015;8:31-35.
20. Tsuchiya S, Kanaya N, Hirata N, Kurosawa S, Kamada N, Edanaga M, Nakayama M, Omote K, Namiki A. Effects of thiopental on bispectral index and heart rate variability. Eur J Anaesthesiol. 2006 Jun;23(6):454-459.
21. Omerbegovic M. Alterations of short-term heart rate variability in peri-induction period of general anaesthesia with two intravenous anaesthetics. Med Arch. 2013;67(4):233-236.
22. Riznyk L, Fijałkowska M, Przesmycki K. Effects of thiopental and propofol on heart rate variability during fentanyl-based induction of general anesthesia. Pharmacol Rep. 2005 Jan-Feb;57(1):128-134.