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CHANGES OF ARTERIAL BLOOD PRESSURE AND HEART RATE DURING INDUCTION OF ANESTHESIA WITH MIDAZOLAM AND FENTANYL. IS ENHANCED BASAL CARDIAC PARASYMPATHETIC TONUS A RISK FACTOR FOR CARDIOVASCULAR INSTABILITY?

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ИЗМЕНЕНИЯ АРТЕРИАЛЬНОГО ДАВЛЕНИЯ И ЧАСТОТЫ СЕРДЕЧНЫХ СОКРАЩЕНИЙ ПРИ ПРИМЕНЕНИИ МИДАЗОЛАМА И ФЕНТАНИЛА ДЛЯ ИНДУКЦИИ АНЕСТЕЗИИ. ЯВЛЯЕТСЯ ЛИ ПРЕОБЛАДАНИЕ ТОНУСА ПАРАСИМПАТИЧЕСКОГО ОТДЕЛА ВЕГЕТАТИВНОЙ НЕРВНОЙ СИСТЕМЫ В ПОКОЕ ФАКТОРОМ РИСКА РАЗВИТИЯ ГЕМОДИНАМИЧЕСКОЙ НЕСТАБИЛЬНОСТИ?

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Актуальность темы. Проведение индукции общей анестезии мидазоламом и фентанилом часто сопровождается изменениями артериального давления и частоты сердечных сокращений. В настоящее время отсутствуют клинические исследования, посвященные изучению связи между тонусом вегетативной нервной системы в покое и развитием гемодинамической нестабильности после индукции анестезии мидазоламом и фентанилом.

Цель исследования: выявить изменения уровня артериального давления и частоты сердечных сокращений при индукции анестезии мидазоламом и фентанилом и проанализировать связь между тонусом вегетативной нервной системы в покое и развитием гемодинамической нестабильности.

Материалы и методы. Было проведено проспективное рандомизированное исследование, которое было одобрено этическим комитетом Государственного Университета Медицины и Фармации имени Николая Тестемицану. У всех участников было получено письменное информированное согласие. Мы обследовали 47 больных с риском по ASA I-II, которым планировались хирургические вмешательства.

Мы провели анализ вариабельности сердечного ритма, основываясь на мониторировании ЭКГ по Холтеру, а также исследовали артериальное давление, частоту сердечных сокращений, наличие аритмий в покое, после премедикации, а также после индукции анестезии мидазоламом 0,2-0,3 мг/кг и фентанилом 1,5 мкг/кг.

Результаты исследования. Индукция анестезии мидазоламом и фентанилом сопровождалась повышением тонуса парасимпатической нервной

системы. Проведенные исследования выявили, что преобладание в условиях покоя тонуса парасимпатической нервной системы является фактором риска развития синусовой брадикардии (OR = 13,1 (95%CI 3,1-54,7, p=0,0002) и артериальной гипотензии (OR = 12,7 (95%CI 2,9 -55,9, p=0,0003).

Выводы. Индукция анестезии мидазоламом и фентанилом сопровождалась развитием артериальной гипотензии и синусовой брадикардии. Преобладание в условиях покоя тонуса парасимпатической нервной системы является фактором риска развития синусовой брадикардии и артериальной гипотензии после индукции анестезии мидазоламом и фентанилом.

Ключевые слова: артериальная гипотензия, синусовая брадикардия, тонус парасимпатической нервной системы.

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Background. Induction of general anesthesia with midazolam and fentanyl is frequently associated with changes in arterial blood pressure and heart rate. At present, there are no clinical studies investigating the relation between basal cardiac autonomic tonus and cardiovascular instability after induction of general anesthesia with midazolam and fentanyl.

The aim of the study was to evaluate the changes of arterial blood pressure and heart rate after induction of general anesthesia with midazolam and fentanyl and to determine if a relationship exists between basal cardiac autonomic tonus and hemodynamic instability.

Materials and methods. A randomized prospective study was performed with approval of Ethic Committee. Written informed consent was obtained from all patients. We enrolled in the study 47 ASA physical status I–II patients scheduled for elective surgical procedures. Heart rate variability by Holter ECG, arterial blood pressure (systolic, diastolic, mean), and heart rate were measured at baseline, after premedication, as well as after induction of general anesthesia with midazolam 0.2-0.3 mg/kg and fentanyl 1.5 mkg/kg

Results of the research. Induction of general anesthesia with midazolam and fentanyl was associated with an increase in cardiac parasympathetic tonus. Our research revealed that increased basal cardiac parasympathetic tonus was a risk factor for development of sinus bradycardia (OR = 13.1 (95%CI 3.1-54.7, p=0.0002) and arterial hypotension (OR = 12.7 (95%CI 2.9 -55.9, p=0.0003).

Conclusions. Induction of general anesthesia with midazolam and fentanyl was associated with arterial hypotension and sinus bradycardia. Increased basal cardiac parasympathetic tonus represents a risk factor for development of arterial hypotension and sinus bradycardia after administration of midazolam and fentanyl for induction of general anesthesia.

Keywords: arterial hypotension, sinus bradycardia, cardiac parasympathetic tonus.

Introduction. Midazolam is a popular agent for sedation and induction of general anesthesia as it has a fast onset and short duration of action with minimal side effects. Midazolam acts on GABA-A receptors which play an important role in regulation of au-

tonomic nervous system. It has anxiolytic, sedative, hypnotic, anticonvulsant, and anterograde amnesia properties [1-4].

The combination of an opioid and midazolam is the most commonly used sedation regimen in gastrointestinal endoscopy [5-8]. Midazolam is a benzodiazepine which has been used successfully with other induction agents to reduce the dose of these drugs, a technique called co-induction [9].

However, it has been reported that midazolam in recommended doses (0.2–0.3 mg/kg) may significantly reduce blood pressure. For this reason, a small-dose of midazolam (less than 5 mg as a rapid bolus) was recommended, but such low doses may not provide adequate level of anesthesia [9-12].

Heart rate variability (HRV) is a widely used method for assessment of autonomic nervous system of the heart in anesthesia and intensive care [13,14]. Controversies still exist over the effects of midazolam combined with fentanyl on the heart rate variability. In most studies midazolam was used in sedative doses. It is generally accepted that small doses of midazolam increase the sympathetic tonus of the heart while high-doses enhance vagal influences on the heart [15-17]. Administration of 0.2-0.3 mg/kg midazolam and 1.5 mkg/kg fentanyl for induction of general anesthesia increased the parasympathetic tonus of the heart [18].

The aim of the study was to determine whether enhanced basal cardiac parasympathetic tonus is more frequently associated with cardiovascular instability after induction of general anesthesia with fentanyl and midazolam.

Materials and methods. We performed a prospective randomized study to evaluate the relationship between basal cardiac autonomic tonus of the heart and the risk for development of cardiovascular instability after induction of general anesthesia with fentanyl and midazolam. The study protocol was approved by the Ethic Committee of the State University of Medicine and Pharmacy "Nicolae Testemiţanu", Chişinău (No.20, 2.02.2016).

Between March 2017 and September 2017, ASA physical status I-II patients aged less than 60 years (to exclude age-related changes of HRV) scheduled for elective surgeries with normal sinus rhythm on ECG were enrolled in the study. We obtained an informed consent from all research participants. Patients with diseases that could affect autonomic cardiac regulation (endocrine, neurological, cardiovascular diseases) were excluded from the study.

In the operating room, the patients were monitored (Holter ECG (Holter TLC 5000, USA)), non-invasive blood pressure, pulse oximetry and capnography). Baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and respiratory rate were recorded. During induction of general anesthesia, oxygen was delivered to maintain SpO_2 above 95%. All patients received 10 ml/kg of crystalloid before induction of anaesthesia.

HRV parameters, heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) and respiratory rate were recorded at baseline (T1), 5 minutes after premedication with Fentanyl 1.0 mkg/kg (T2) and 5 minutes after induction of general anesthesia with midazolam 0.2-0.3 mg/kg and fentanyl 1.5 mkg/kg (T3). If after receiving midazolam and fentanyl, patients developed bradypnea or apnea, the mask ventilation was initiated at a rate of 14-16 breaths/min and tidal volume of 7-8 ml/kg, an important requirement for correct registration and analysis of HRV.

HRV parameters were analyzed by Holter computerized system. HRV was interpreted according to the recommendations of the *Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology* [19].

Sinus tachycardia was considered in any patient who had a heart rate more than 100 beats/min, and sinus bradycardia – a heart rate less than 60 beats/min.

We considered systolic arterial hypertension when SBP was more than 140 mmHg or an increase in SBP of *more* than 20% from *baseline values*, systolic arterial hypotension – when SBP was less than 90 mmHg or a *decrease* in SBP *more* than *20*% below *baseline,* and diastolic hypotension – when DBP was less than 60 mmHg or a *decrease* in DBP *more* than 20% below *baseline.*

Statistical analysis of the results was performed using GraphPad Prism 6 (GraphPad Software, San Diego, California, SUA). Values with parametric distribution were analyzed by t-pair and repeated measures ANOVA tests. Values with non-parametric distribution were analyzed by Wilcoxon and Friedman tests. The Fisher's exact test was used to compare categorical variables.

Results are expressed as 95% confidence interval of odd ratio (parametric data) and median with interquartile range (IQR, non-parametric data). A p value of less than 0.05 was considered statistically significant.

Results and discussions. The study group consisted of 47 patients (27 females and 20 males), aged 38±12 years. The mean body mass index was 24.5±3.3 kg/m^2 (it ranged between 16.7 and 29.7 kg/m^2).

Analysis of HRV showed that 5 minutes after administration of midazolam and fentanyl for induction of general anesthesia the proportion of patients with enhanced sympathetic heart tonus decreased by 38,2%. Another important finding was a remarkable increased proportion of patients with enhanced parasympathetic heart tonus, more than half from the study group, 53.1%) (Fig.1).The results of this study were published in another report [18].

There were *no significant* changes in SBP, DBP, MAP and HR after premedication with fentanyl (1,0 mcg/kg), but after induction of general anesthesia with midazolam 0,2-0,3mg/kg and fentanyl 1,5 mkg/kg, SBP significantly decreased by 20,6% (from 128,8 mmHg at T2 to 102,4 mmHg at T3; p=0,001), DBP – by 27,8% (from 77,8 mmHg at T2 to 56,2 mmHg at T3; p<0,001), MAP – by 24,3% (from 97,3 mmHg at T2 to 73,7 mmHg at

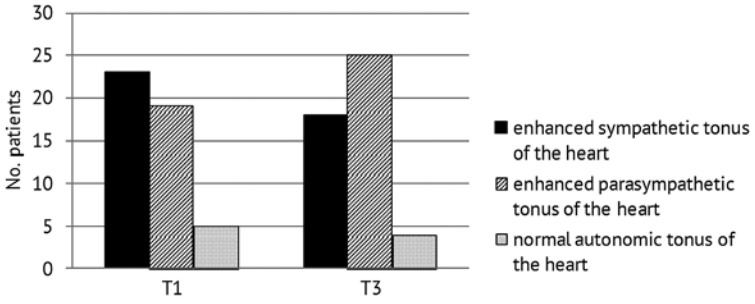

Fig. 1. Number of patients with enhanced cardiac sympathetic, parasympathetic tonus and normal cardiac autonomic tonus at rest and after induction of general anesthesia with midazolam and fentanyl.

Table 1

Changes in blood pressure and heart rate after premedication and induction of general anesthesia

Parameters	T1	T2	T3	p
SBP	135.0 (130.5-139.5)	128.8 (124.3-133.4)	102.4 (97.7-107.1)	0.001
DBP	82.9 (79.2-86.6)	77.8 (74.4-81.3)	56.2 (52.7-59.7)	0.001
MAP	103.4 (99.3-107.4)	97.3 (93.7-100.9)	73.7 (69.7-77.7)	0.001
HR	75.5 (72.1-78.9)	73.8 (70.4-77.1)	60.5 (56.1-66.8)	0.03

Blood pressure and HR values are represented as mean and 95% CI

T3; p=0,001), and HR – by 18,0% (from 73,8 beats/min at T2 to 60,5 beats/min at T3; p=0,03), (table 1).

After induction of general anesthesia most patients (24 patients – 51.0%) developed either isolated diastolic or combined systolic and diastolic hypotension (Fig.2). Twelve patients had isolated diastolic hypotension and another 12 – combined systolic and diastolic hypotension. The minimal SBP was 74 mmHg, the minimal DBP was 38 mmHg, and minimal MAP was 53 mmHg. After administration of midazolam and fentanyl, only 9 patients (19.1%) developed arterial hypertension, but in 7 patients elevation of blood pressure was transient (1 to 2 minutes), followed by normalization of blood pressure or even arterial hypotension. Persistent arterial hypertension was present only in 2 patients, and they had increased cardiac sympathetic tonus both at rest and after induction of general anesthesia (Fig. 2). Arterial hypotension was corrected with fluids, and none of the patients required vasopressor support.

It is worth to mention that most patients (66.6%) who developed hypotension after administration of midazolam and fentanyl had increased parasympathetic heart tonus after induction of general anesthesia as well as at rest.

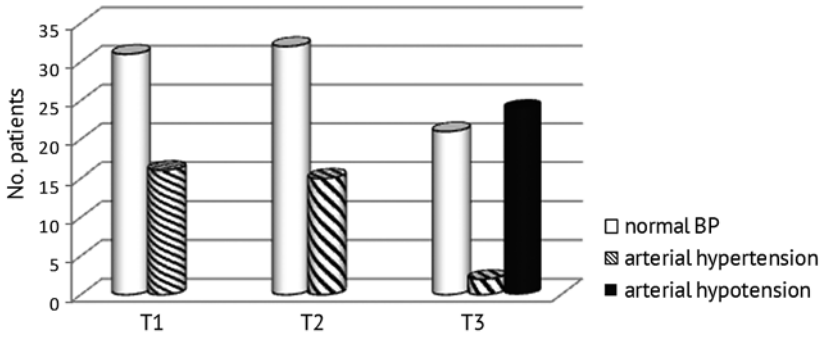

Fig. 2. Number of patients with normal BP, arterial hypertension and arterial hypotension at rest, after premedication and induction of general anesthesia

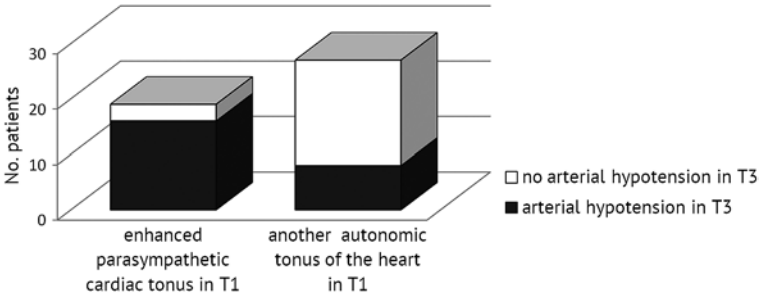

Fig. 3. Relationship between autonomic cardiac tonus at rest and development of arterial hypotension after induction of general anesthesia with midazolam and fentanyl

Sixteen of the 19 patients with enhanced basal parasympathetic tonus of the heart developed arterial hypotension after administration of fentanyl and midazolam. On the other hand, only 8 of the 28 patients with normal basal autonomic cardiac tonus or enhanced basal sympathetic cardiac tonus, developed arterial hypotension after induction of general anesthesia.

It can therefore be concluded that enhanced basal parasympathetic tonus of the heart is a risk factor for development of arterial hypotension after administration of midazolam and fentanyl (OR=12.7 (95% CI 2.9-55.9); p=0.0003) (Fig. 3).

After induction of general anesthesia, sinus bradycardia occurred in 21 patients (44.7%) (Fig.4). Four patients developed severe bradycardia which was corrected with atropine sulphate. The slowest heart rate was 24 beats/min.

After induction of general anesthesia with midazolam and fentanyl, cardiac arrhythmias were observed in 7 patients (14.9%): 5 patients had single supraventricular or ventricular extrasystole, one patient experienced multiple ventricular extrasystoles and one patient – sustained sinus bradycardia. It is worth to mention that 6 of the 7 patients who developed cardiac arrhythmias, had increased basal cardiac sympathetic tonus which persisted after induction of general anesthesia. The patient who developed severe, sustained sinus bradycardia had increased cardiac parasympathetic tonus both at rest and after administration of midazolam and fentanyl (Fig. 4).

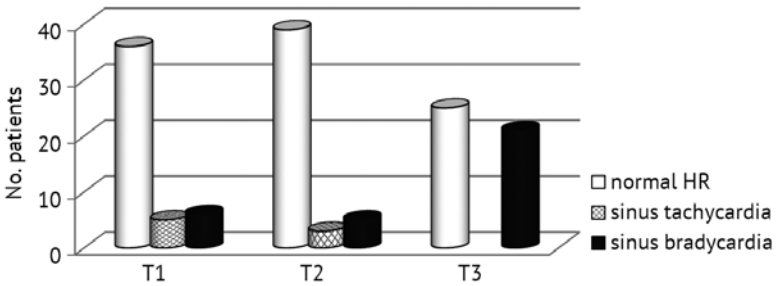

Fig. 4. Number of patients with normal HR, sinus tachycardia and sinus bradycardia at rest, after premedication and induction of anesthesia

It is important to mention that 17 (80.9%) of the 21 patients who developed sinus bradycardia after administration of midazolam and fentanyl had increased parasympathetic heart tonus after induction of general anesthesia, and 15 patients – enhanced basal parasympathetic cardiac tonus.

Fifteen of the 19 patients with enhanced basal cardiac parasympathetic tonus developed sinus bradycardia after administration of midazolam and fentanyl, while only 6 of the 28 patients who had normal basal autonomic tonus of the heart or enhanced basal sympathetic tonus of the heart developed sinus bradycardia after induction of anesthesia. Statistical analysis using Fisher's exact test revealed that enhanced parasympathetic cardiac tonus at rest is a risk factor for development of sinus bradycardia after administration of midazolam and fentanyl (OR=13.1, 95%CI 3.1-54.7; p= 0.0002) (Fig. 5).

Although there are many studies that evaluated the effect of midazolam on cardiac *autonomic nervous system* using HRV [15-18], relationship between cardiac autonomic tonus at rest and the risk for cardiovascular instability after induction of anesthesia with midazolam and fentanyl have not been investigated.

Many studies have examined the hemodynamic changes after administration of midazolam, but in most of them midazolam was administered for sedation [5-7,11,20]. Only few studies investigated the hemodynamic changes after induction of anesthesia with midazolam, and it is important to note that in most of these studies midazolam was used as an *anesthesia* co-*induction agent* [9,10,12].

In a recent meta-analysis of five randomized clinical trials involving 552 patients, Zhang R. et al. found that sedation during gastrointestinal endoscopy with midazolam was safer than propofol (propofol showed higher incidence of hypotension than midazolam) [7]. Tsai H.C. et al. [6] in another meta-analysis of five randomized studies conducted between 2003 and 2012 analyzed the efficacy and safety of midazolam sedation in cirrhotic patient undergoing endoscopy. Authors found that the incidence of bradycardia was 2.86% and 13 of the 182 patients exhibited arterial hypotension. Frolich M.A. et al. showed that intravenous infusion of midazolam 3.0-5.0 mg/h didn't change significantly SBP, DBP, MBP and HR in healthy volunteers when compared with propofol and dexmedetomidine [11]. In addition, a recent study by Uzman S. et al., proved that sedation with the combination of 0.05 mg/kg midazolam and 0.4 mg/kg meperidine is safer than with 1 mg/kg propofol. None of the patients in midazolam group developed arterial hypotension or bradycardia [5].

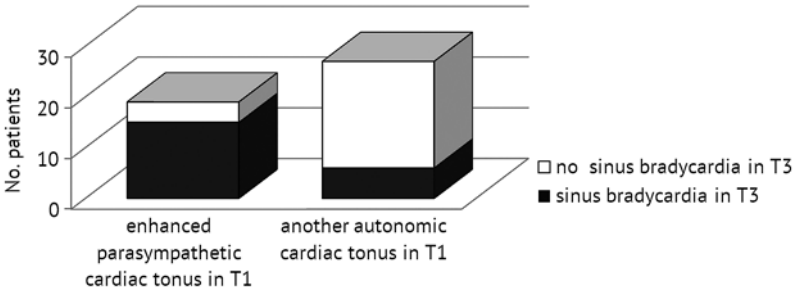

Fig. 5. Relationship between autonomic cardiac tonus at rest and development of sinus bradycardia after induction of general anesthesia with midazolam and fentanyl

Ab Rahman N.H. et al. examined the safety of sedation analgesia with fentanyl 1.0 mcg/kg and midazolam 0.1 mg/kg in 20 patients in emergency department. Even though SBP, DBP and MAP dropped, the changes were not statistically significant [20]. We cannot compare their results with ours as we used higher doses of midazolam (0.2-0.3 mg/kg).

There are several studies investigating midazolam for induction of general anesthesia. Choi Y. et al. [12] analyzed the hemodynamic effects of midazolam 2.0-4.0 mg used as induction agent for rapid sequence intubation in emergency department. They observed a 10% drop in mean SBP; 19.5% of patients developed arterial hypotension. Patients older than 70 years were more likely to develop hypotension. In another study, Han D. et al. proved that the combination of midazolam (0.2 mg/kg) and sufentanyl (1.0 mkg/kg) is a safe method for induction of general anesthesia for cardiac surgery in children [10]. Even though HR decreased after intubation, this combination had more favorable effects on hemodynamics when *compared with sevoflurane*.

In our study, we noted a greater decrease in DBP than SBP (27.8% vs 20.6%), although all patients received 10 ml/kg crystalloids before induction of general anesthesia. Sinus bradycardia was observed in 44.7% of patients 5 minutes after administration of midazolam and fentanyl; HR decreased by 18.0% following induction of anesthesia. Normal HR after induction had 53.2% of patients.

Our study revealed that enhanced basal cardiac parasympathetic tonus represents a risk factor for development of sinus bradycardia and arterial hypotension after administration of midazolam and fentanyl for induction of general anesthesia.

Conclusions. Induction of general anesthesia with midazolam and fentanyl is frequently associated with arterial hypotension and sinus bradycardia. Enhanced parasympathetic tonus of the heart at rest is a risk factor for development of arterial hypotension and sinus bradycardia after administration of midazolam and fentanyl.

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