Assessment of xenon-induced depth of hypnosis according to Kugler's scale in elderly and senile patients undergoing knee replacement surgery: a prospective open-label cohort study

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Abstract

INTRODUCTION. Anesthesia with xenon is characterized by stable hemodynamic parameters, cardio- and neuroprotection preferable in elderly. Assessment of the depth of hypnosis remains challenging. The Kugler classification based on electroencephalogram has been suggested for such assessment. **OBJECTIVES.** To assess the feasibility of Kugler scale for objective assessment of the depth of hypnosis induced by xenon alone or in combination with narcotics and regional anesthesia during knee arthroplasty in elderly. **MATERIALS AND METHODS.** The study included 57 patients divided into 2 groups. In group 1, general anesthesia with xenon was performed, fentanyl and femoral nerve block were used for pain control. In group 2, xenon anesthesia was performed in combination with femoral and sciatic nerve block. The depth of hypnosis was monitored using EEG and matched with the Kugler scale. Also, the bispectral index (BIS) was recorded. **RESULTS.** The baseline alpha rhythm level did not differ significantly between the groups. At xenon concentration of 40 %, the depth of hypnosis reached D2 stage in group 1 and D1 in group 2 patients, while at 55 % and above concentration it was D2 in both groups. Fentanyl 0.39 ± 0.07 mg increased the delta rhythm (δ) by an average of 19.08 %, which corresponded to the estimated reduction in the effective xenon concentration of approximately 20 %. Analysis of delta-rhythm decrease and BIS values using the Spearman's rank. **CONCLUSIONS.** In elderly patients undergoing knee arthroplasty under combined anesthesia, stage D2 according to Kugler scale (proportion of δ-rhythm more than 50 %) is achieved at xenon concentration of 55 %

Оценка глубины угнетения сознания ксеноном по шкале Kugler у пациентов пожилого и старческого возраста при эндопротезировании коленного сустава: проспективное открытое когортное исследование

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Реферат

АКТУАЛЬНОСТЬ. Анестезия ксеноном характеризуется стабильностью гемодинамических показателей, кардиопротективными, нейропротективными свойствами, что предпочтительно у пациентов пожилого и старческого возраста. Нерешенной проблемой остается оценка глубины угнетения сознания. Есть данные о возможности ее оценки по шкале Kugler на основании анализа электроэнцефалограммы (ЭЭГ). **ЦЕЛЬ ИССЛЕДОВАНИЯ.** Оценить возможность применения шкалы Kugler на основании ЭЭГ как алгоритма объективной оценки глубины угнетения сознания ксеноном в комбинации с наркотическими анальгетиками или без них, в сочетании с регионарной блокадой во время операции эндопротезирования коленного сустава у пациентов пожилого и старческого возраста. **МАТЕРИАЛЫ И МЕТОДЫ.** Включено 57 пациентов. Пациенты разделены на 2 группы, в 1-й проводили общую анестезию ксеноном, для обезболивания использовали фентанил и блокаду бедренного нерва, во 2-й анестезию проводили в сочетании с блокадой бедренного и седалищного нервов. Глубину угнетения сознания мониторировали ЭЭГ с расшифровкой и сопоставлением со шкалой Kugler, регистрировали биспектральный индекс (BIS). **РЕЗУЛЬТАТЫ.** При концентрации 40 % в группе 1 уровень глубины угнетения сознания — D2, в группе 2 — D1, при 55 % и выше в обеих группах — D2. Фентанил в дозе 0,39 ± 0,07 мг увеличивал дельта-ритм (δ) на 19,08 %, что соответствовало снижению эффективной концентрации ксенона ≈20 %. Анализ снижения δ-ритма и BIS при помощи ранговой корреляции Спирмена определил сильную связь в группе 1 (r = –0,78;

without narcotics and at concentration of 40 % with fentanyl. The diminished correlation between δ-rhythm and BIS in group 2 and no difference in decrease of BIS suggests that BIS is less accurate for determining the depth of hypnosis during xenon monoanesthesia.

R^2 = 60 %), среднего уровня в группе 2 (r = –0,61; R^2 = 37 %), различия связаны с фентанилом в группе 1. Снижение BIS при сравнении групп не достигло достоверно значимого уровня (p > 0,05). **ВЫВОДЫ.** У пациентов пожилого и старческого возраста при эндопротезировании коленного сустава в условиях сочетанной анестезии ксеноном и блокады периферических нервов стадия D2 по шкале Kugler (доля δ-ритма более 50 %) достигается при концентрации ксенона 55 % в группе без использования наркотических анальгетиков и при концентрации 40 % в случае болюсного введения фентанила. Ослабление силы связи δ-ритма и BIS в группе 2 и отсутствие достоверной разницы снижения BIS говорит о возможности менее точного определения уровня угнетения сознания BIS при моноанестезии ксеноном.

KEYWORDS: xenon, EEG, intraoperative awareness, knee replacement, anesthesia safety

КЛЮЧЕВЫЕ СЛОВА: ксенон, интраоперационное пробуждение, электроэнцефалография, ЭЭГ, эндопротезирование, замена коленного сустава, анестезия, безопасность

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Introduction

Anesthesia with xenon is characterized by rapid onset and short duration, stable intraoperative hemodynamic parameters [1], cardio- [2] and neuroprotective [3] properties, which makes it preferable in elderly and senile patients. Xenon-based general anesthesia combined with peripheral femoral and/or sciatic nerve block during knee arthroplasty may be less associated with side effects and complications. Nerve blockade avoids the undesirable effects of opioid analgesics in older patients and reduces the hemodynamic fluctuations in the intraoperative period due to a more stable analgesic profile [4].

However, despite the advantages of xenon, there are several unresolved problems of its use in anesthesiology. In particular, this refers to the intricacies of reliable assessment of the depth of hypnosis, which is directly related to the problem of general anesthesia awareness. In studies on the use of the bispectral index (BIS) for monitoring the depth of hypnosis during xenon anesthesia, controversial results were obtained that do not allow using this method to monitor awareness during general anesthesia. In her study, Myasnikova V. showed that anesthesia with xenon at concentration of 48–55 % significantly reduced BIS down to 46–56 during ophthalmic surgery, however narcotic analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) were used throughout the surgery which could have an additional effect on BIS values [5]. In a study using xenon anesthesia in neurosurgery for craniotomy to remove brain neoplasms, the BIS index level was within safe range, but 70 % of the patients had epilepsy and were on anticonvulsants, while narcotic analgesics were also used during surgical treatment along with NSAIDs, which could alter the EEG pattern and BIS level [6]. Similar data were obtained in earlier works of other authors, where various techniques of monitoring the depth of hypnosis showed convincing results in xenon anesthesia, but had limitations such as age, concomitant use of narcotic analgesics, benzodiazepines, anticonvulsants in the perioperative period, or diseases that could affect the baseline EEG [7-11]. The variation of the parameters is due to the fact that EEG monitoring methods developed for anesthesia were originally validated to assess the effects of anesthetics interacting with gamma-aminobutyric acid receptors (GABA receptors) and are not designed to monitor the depth of hypnosis when using anesthetics with N-methyl-D-aspartate (NMDA)-antagonistic properties (ketamine, xenon) [12]. Given these circumstances, further collection of native intraoperative EEG monitoring data in combination with existing techniques for subjective and objective assessment of consciousness level seems to be a promising way to create a basis for the development of machine methods for controlling the depth of anesthesia with xenon. The technique used in the Narcotrend EEG monitor validation study by Schultz et al. (2002) could serve as an example of such an approach. The authors compared visual and automatic classification of EEG data on the Kugler scale during propofol anesthesia and obtained a 92 % match of visual and automatic assessments (Spearman rank correlation, $r = 0.9$) [13]. In a similar study with xenon, the authors found an even higher correlation between visual and automatic assessment ($r = 0.957$), but also noted a direct association of low-frequency range EEG activity (delta waves) with very deep stages of anesthesia, in contrast to propofol anesthesia. According to the authors, EEG monitoring should be a mandatory component of anesthesia machines when using xenon anesthesia [14].

Objectives. The study aimed to assess the feasibility of using the EEG-based Kugler scale as an algorithm for objective assessment of depth of hypnosis induced by xenon alone or in combination with narcotic analgesia combined with regional block anesthesia during knee arthroplasty in elderly and senile patients.

Materials and methods

This prospective open-label cohort study was conducted at the Federal State Budgetary Institution Pirogov National Medical and Surgical Center, Ministry of Health of the Russian Federation). The study period was 1 year 8 months (02.2019–10.2020). Patient cohort included those with osteoarthritis of knee joints who had indications for surgical treatment (total knee arthroplasty).

The study was approved by the local ethical committee of the Institute for Advanced Medical Education of the Pirogov Research Medical Center of the Ministry of Health of Russia (Protocol No. 11 dated November 26, 2018) and was conducted as a part of the research work on synchronization of intraoperative records and expert analysis of BIS monitor parameters of depth of hypnosis, EEG and ECG during general anesthesia.

The inclusion criteria were:

- Age 60 years and older.
- Validated Montreal Cognitive Scale (MoCA) score of 26 or higher.
- No history of diseases and operations that could alter the amplitude and frequency characteristics of the electroencephalogram (acute cerebrovascular accident with persisting neurological deficit, epilepsy, brain neoplasms).
- Self-signed informed consent to participate in the study.

The non-inclusion criteria were:

- Bradycardia (heart rate < 60 bpm of various origins).
- History of diseases causing elevated intracranial pressure (brain neoplasms, traumatic brain injury, hydrocephalus of various etiologies).

Based on the inclusion and non-inclusion criteria, 57 patients were enrolled in the study. They were divided into two groups; the enrollment in the study groups took place sequentially in chronological order according to the study design and objectives.

In both groups medical xenon (OOO AKELA-N, Russia) in combination with peripheral nerve block of the lower extremities was used for anesthesia. Xenon anesthesia was performed using a closed circuit Felix Dual (Air Liquide Medical Systems, France) machine. Averaged concentration of xenon in the circuit was calculated in automatic eco-mode, the supply of fresh mixture was carried out fractionally when the xenon concentration decreased by 5–7 % of the predefined one which was necessary to consider while setting the target concentrations. To perform peripheral nerve blocks in both groups without nerve injury we used a neurostimulator (Stimuplex HNS 12, BBraun, Germany) with a special needle for neurostimulation (Stimuplex A, BBraun, Germany) and ultrasound (US) navigation (Fujifilm Sonosite Edge II, USA) for visual positioning of the needle tip and monitoring the anesthetic distribution.

Based on the aim of the study the patients were divided into two groups. Group 1 included 39 patients who received anesthesia with xenon during the entire surgical intervention. In order to provide analgesia, we used isolated femoral nerve block; if there were signs of insufficient anesthesia, we administered an intravenous bolus of fentanyl.

Prior to induction anesthesia, femoral nerve block was performed by puncturing the skin with a neurostimulation needle in the projection of the femoral nerve trunk under ultrasound control, considering the anatomical landmarks. The following neurostimulation parameters were used: initial intensity 1 mA, duration 0.1 ms, frequency 2 Hz. As the response from the nerve increased, the neurostimulation intensity was stepwise reduced to 0.4–0.3 mA, and then a solution containing ropivacaine 0.5 % 5 ml and lidocaine 1 % 5 ml was injected perineurally.

Propofol 2–2.5 mg/kg was used to induce anesthesia. After myorelaxant administration (rocuronium 0.5 mg/kg), a Vogt Medical (Germany) laryngeal mask was placed, and ventilation was started with FiO_2 100 % for 5 min to denitrogenize the patient. Then xenon was fed into the breathing mixture in Felix Dual eco-mode until the target concentration of 60 % was reached.

In group 2 (18 patients), the goal of the researchers was to assess the effect of anesthesia with xenon without fentanyl on EEG. Therefore, the anesthesia regimen was altered, femoral nerve block was supplemented with sciatic nerve block via lateral access, using similar modes of neurostimulation, volume, and composition of anesthetics. After induction, desflurane was used to maintain anesthesia at the initial stage; the depth of hypnosis was controlled by the bispectral index (BIS) (Aspect Medical Systems, USA) with the target value within the range of 40–60. After the traumatic stage of surgery, during preparation for cementing of the endoprosthesis components, desflurane delivery was stopped and the fresh mixture flow rate was increased up to 6 l/min for 5 min with FiO_2 100 %, in order to eliminate the anesthetic and denitrogenize. Then, in an automatic eco-mode of Felix Dual machine, xenon supply was started up to the target concentration of 65 %, following the recommended estimated concentrations. In order to control the level of consciousness and exclude possible episodes of intra-anesthetic awareness during anesthetic change, BIS-monitoring was performed continuously in addition to standard assessment of clinical signs, blood circulation and gas exchange parameters. Taking into account the method of anesthesia in this group, we considered that an acceptable BIS level during anesthetic change was ≤ 70 %, which ensured superficial sedation sufficient for non-traumatic stages of surgical intervention. In addition, all patients were interviewed using the Brice questionnaire in the postoperative period in order to identify possible episodes of awareness during general anesthesia [15]. The characteristics of participants are presented in Table 1.

The included patients of both groups had no significant differences and were comparable in height, weight, and sex. Significant difference in age (p = 0.008) was demonstrated; given the sequential recruitment of groups at different time periods using the same inclusion/non-inclusion criteria, the researcher could not influence this factor.

Anesthesia duration did not differ significantly in both groups (90 [80–95] min, 80 [70–94] min, respectively, p = 0.211), there were no intraoperative complications and significant abnormalities in monitored gas exchange and blood circulation parameters compared to the baseline values. Intraoperative fentanyl consumption was 0.39 ± 0.07 mg (mean 4 μg/kg) in group 1 and 0 mg in group 2.

In both groups during the whole anesthesia period EEG was recorded using a helmet with gel electrodes according to the international “10–20 % system” and the International Federation of Societies for Electroencephalography and Clinical Neurophysiology standard from frontal (F), central (C), temporal (T), parietal (P) and occipital (O) leads with automatic suppression of artifacts. During digitized EEG recording using Neurotravel software (Ates Medica Soft, Moscow) labels were placed for the beginning and the end of xenon supply and the percentage composition of xenon mixture. After surgery, retrospectively, the EEG data were converted into the percentage composition of rhythms at different stages of anesthesia using Axes Graphics software (Ates Medica Soft, Moscow) and analyzed by a certified specialist.

The Kugler scale (Table 2) was used to estimate the depth of hypnosis when interpreting the EEG. This scale was proposed in 1981 for EEG-based visual assessment, where the phases of hypnosis were divided into 16 stages depending on the predominance of the EEG pattern at the time of recording [16].

Statistical analysis

Statistical analysis was performed using STATISTICA version 10.0 software. The normality of the distribution of quantitative characteristics was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. If the distribution was not normal, the data were presented as median (Me) and the interquartile interval (Q1;Q3) or the 95 % confidence interval (95 % CI). Qualitative variables are presented as absolute and relative frequencies (percentages), n (%). Mann-Whitney U-test was used to determine the significance of differences between the groups in quantitative characteristics. Chi-square test (χ^2) was used to compare qualitative characteristics. If absolute frequencies were less than 10 but greater than 5, Yates’ criterion for continuity

Table 1. Characteristics of patient groups

Variable	Group 1 (n = 39)	Group 2 (n = 18)	p
Females, n (%)	29 (74.3)	16 (88.8)	0.3
Age, years [Me (Q1–Q3)]	70 (66–77)	63 (61–69)	0.008
Height, cm [Me (Q1–Q3)]	165 (159–173)	160 (158–166)	0.183
Weight, kg [Me (Q1–Q3)]	89 (83–94)	85 (75–90)	0.108
BMI, kg/m^2 [Me (Q1–Q3)]	31.2 (29.7–33.7)	32.2 (30–34)	0.850
Comorbidities			
Coronary heart disease, n (%)	29 (74.3)	18 (100)	0.223
Essential hypertension, n (%)	32 (82.0)	18 (100)	0.085
Diabetes mellitus, n (%)	13 (33.3)	3 (16.6)	0.225
Heart rhythm disorders (various types), n (%)	13 (33.3)	4 (22.3)	0.537

Note. Mann-Whitney test was used to compare quantitative variables. For qualitative variables, χ^2 test (for more than 5 variables in the group) and Fisher exact test (for 0–5 variables in the group) were used.

Table 2. Kugler scale

Clinical phase of anesthesia	Expert visual description	Stage
Awake	A0: awakening; dominant α rhythm, low β, θ, δ	0
	A1: awakening with minor sedation; α rhythm ≤ 15 %, enhanced θ, low δ, β	1
	A2: α waves low and rare, θ rhythm ≤ 30 %	2
Somnolence	B0: somnolence to superficial sedation; θ waves ≤ 30 % together with low α, β, δ	3
	B1: moderate θ waves and enhanced amplitude of δ, β	4
	B2: vertex waves, moderate θ, low δ	5
Superficial narcosis, sedation	C0: superficial narcosis; diffuse increasing θ, enhanced δ rhythm; low β in occipital channels and K-complexes after sensory stimulation	6
	C1: accelerated α rhythm (“sleep spindles"), K-complexes, low δ	7
	C2: frequent β (frontal), temporal transient increased δ waves, low K-complexes	8
Moderate narcosis, mild suppression of cortex	D0: moderate narcosis; δ waves ≤ 30 %, decreasing β, rare K-complexes	9
	D1: high δ waves ≤ 50 %, low β, moderate θ	10
	D2: dominant slow δ waves ≤ 80 %, low θ, β	11
Deep narcosis, moderate suppression of cortex	E0: very deep narcosis: slow 2–3/s δ increasing, 100–300 μV, no K-complexes	12
	E1: slow 1–3/s δ increasing, 100–400 μV, no K-complexes	13
	E2: continuous slowing 0.5–3/s of δ wave, 100–400 μV, no K-complexes	14
Very deep narcosis, total suppression of cortex, coma	F: coma. Bilateral suppression, irregular waves 0.5–3/s, δ increases 100–400 μV with overlapping 7–9 /s in 20–80 μV series and increasing 12–14/s in 10–30 μV series.	15

was used. If the absolute frequencies of the qualitative indicator in the group were small (from 0 to 5), Fisher's exact test was used to evaluate the significance of differences. Spearman rank correlation coefficient and the coefficient of determination (R2) were used to evaluate the relationship between the phenomena. Differences were considered significant at $p < 0.05$.

Results

During surgery, the target BIS level was within 40–60 % (with an exception of the period of anesthetic change in Group 2, where BIS ≤ 70 % was considered acceptable) during the denitrogenization stage in both groups and during anesthetic change in Group 2, no clinical and hemodynamic signs of awakening were registered.

After processing the EEG in both groups, we obtained the data shown in Fig. 1–2. In both groups, the values obtained before induction anesthesia were considered as the baseline EEG values. The α-rhythm was predominant at baseline in all patients with its level being 39.5 % in group 1 and 34.4 % in group 2 ($p = 0.18$). The decrease in the amplitude of the predominant initial level of α-rhythm in patients before induction of anesthesia (normal α-activity ≥ 50 %) can be explained, in our opinion, by increased functional brain activity (intense attention, anxiety, restlessness) before the beginning of surgery in the operating room.

After induction of anesthesia, the true α-rhythm disappeared, and later decreasing waves of spectral activity in the α-frequency range were present. The level of β-rhythm (active wakefulness) decreased after induction of anesthesia and was approximately 0.1 % during the whole period, which had no scientific value. K-complexes and sleep spindles, usually occurring in the 2nd stage of sleep, were considered as integral part of the sleep pattern, which after digital processing fell either into the low-frequency β-rhythm range or into the high-frequency α-rhythm (12–15 Hz), did not have a separate information component, whereas the most significant changes in EEG activity depending on xenon concentration were parameters of the spectral power of theta (θ) and delta (δ) rhythms.

The changes in the activity of the slower θ-rhythm with the 3.5–7.5 Hz frequency are shown in Fig. 1.

As Fig. 1 shows, the θ-rhythm activity increase occurred only until xenon concentration reached 40 %, then θ-rhythm activity began to decrease, which was associated with the patient's transition to a deeper hypnosis and ongoing slowdown of electrophysiological activity of the brain.

Starting with a concentration of 30 %, a definite increase in the EEG activity of the slow brain rhythm with a frequency of 0.5–4 Hz (δ-rhythm) was observed, which was the focus of further research interest.

Comparison of EEG rhythm activity between the groups shows that δ-rhythm activity increased with rising xenon concentration in the breathing mixture and reached average values of 71.09 % in Group 1 at xenon concentration of 60 %, while approximate δ-activity values of 69.2 % in Group 2 were achieved only at 65 % xenon concentration. We attribute this difference to the use of fentanyl (see Fig. 2, Table 3).

To determine the relationship between xenon concentration, depth of hypnosis, and EEG changes, we compared the data obtained with the validated levels on the Kugler scale (Table 3). The value of the depth of general anesthesia according to the Kugler scale was established based on the median of the δ-rhythm fraction

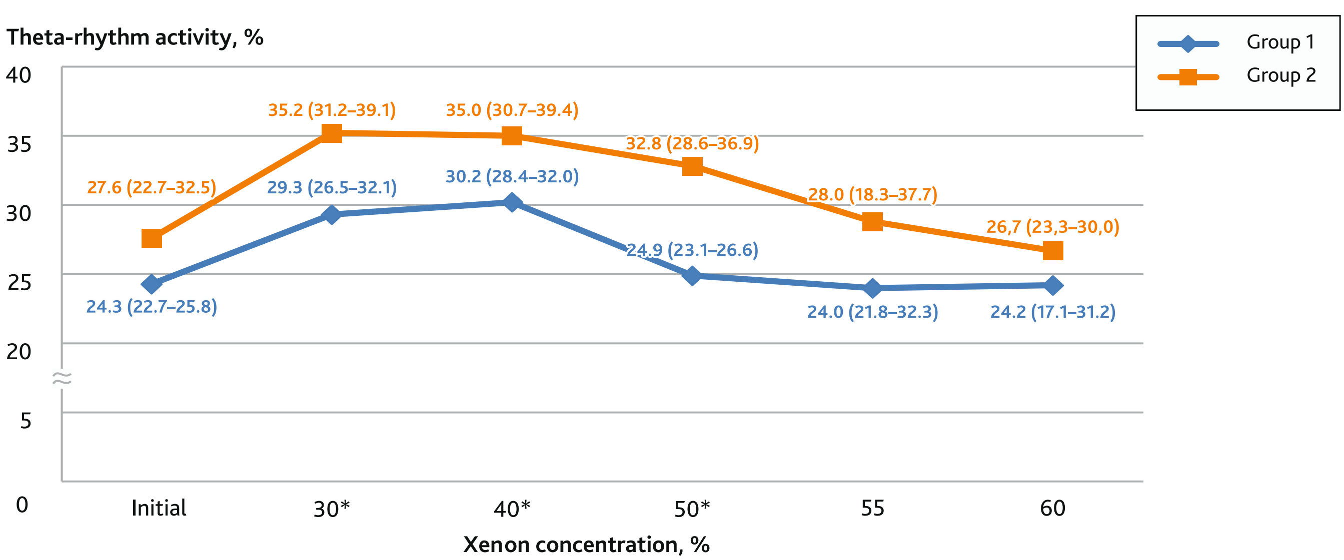

Fig. 1. Relationship between theta-rhythm activity and xenon concentration

Note. The data are presented as Me and 95% CI.

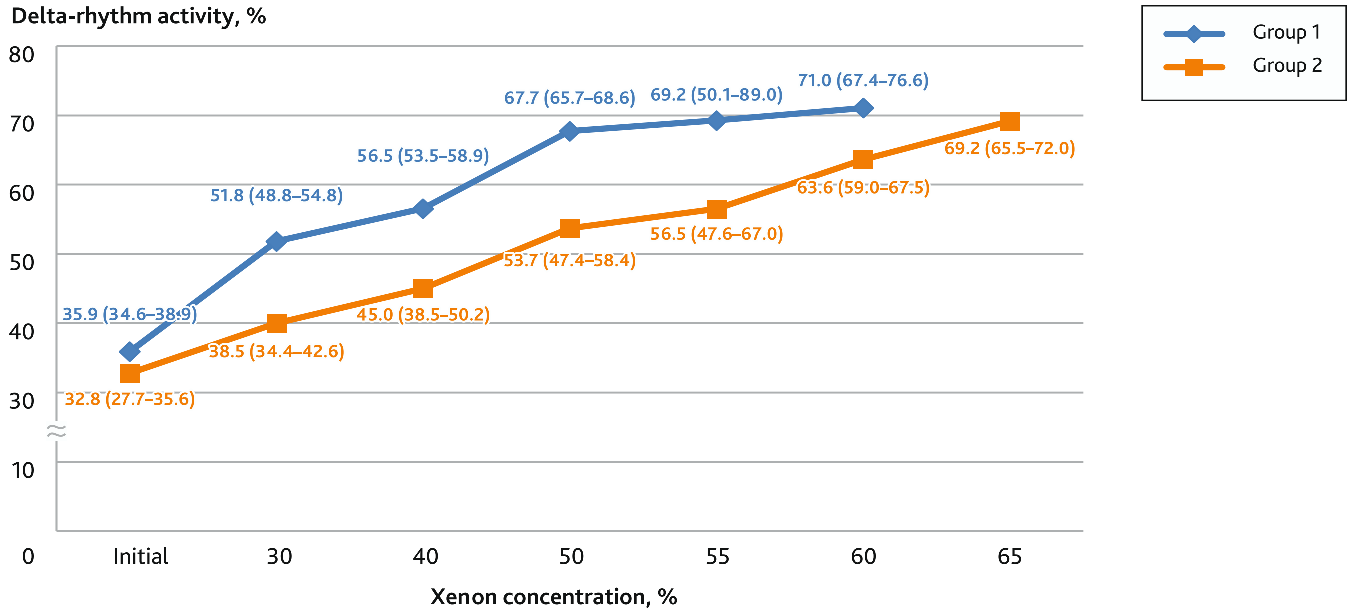

Fig. 2. Relationship between the δ-rhythm and xenon concentration

Note. The data are presented as Me and 95% CI.

in the spectrum for the specified xenon concentration, provided that the extreme value of the 95 % CI was not lower than the one set in the scale for the given level.

As we can see from Table 3, with a gradual increase in xenon concentration there was a trend towards a decrease in BIS values. When assessed by Spearman rank correlation coefficient, there was an inverse correlation between BIS index changes and δ-rhythm with $r = -0.78$ (strong) for group 1 and $r = -0.61$ (intermediate strength) for group 2 with the coefficient of determination of 60 % and 37 %, respectively. This difference could be due to the use of fentanyl, which has an additional effect on the depth of hypnosis, in group 1. In group 2 (xenon monoanesthesia), the correlation analysis showed that the BIS index less accurately reflected the depth of hypnosis. This was further confirmed by lack of significant differences in BIS index

Table 3. Comparison of δ-rhythm parameters with Kugler and BIS levels of depth of hypnosis

Xenon concentration on inspiration, %	BIS* (group 1)	BIS* (group 2)	*p* value for the intergroup difference in BIS	Percentage of δ-rhythm* (group 1)	Percentage of δ-rhythm* (group 2)	P value for the intergroup difference in δ-rhythm	Mean difference of δ-rhythm between the group, %	Depth of hypnosis according to the Kugler scale	
								Group 1	Group 2
30	55.2 (50.8; 60.5)	59 (51.9; 62.9)	0.121	51.8 (48.8; 54.8)	38.5 (34.4; 42.6)	< 0.001	25.67	D1	D0
40	49.5 (47.7; 51.1)	47.5 (46.1; 56.9)	0.772	56.5 (53.5; 58.9)	45 (38.5; 50.2)	< 0.001	20.35	D2	D1
50	46 (43.5; 47.2)	49.5 (42.5; 53)	0.257	67.7 (65.7; 68.6)	53.7 (47.4; 58.4)	< 0.001	20.67	D2	D1
55	42 (38; 45.5)	46.5 (40.9; 51.1)	0.103	69.2 (65.1; 73.6)	56.5 (49.6; 67)	0.068	18.35	D2	D2
60	41 (39.6; 44.5)	44 (39.9; 50.4)	0.283	71 (67.4; 76.6)	63.6 (59.0; 67.5)	0.090	10.4	D2	D2
65	—	43.5 (40.8; 50.1)	—	—	69.2 (65.5; 72)	—	—	—	D2

* Values are given as Me and 95 % CI.

values between the study groups in respect to fentanyl use at different xenon concentrations.

Percentage of δ-rhythm activity proved to be a more sensitive index directly related to xenon concentration in the range from 30 to 65 % and was to some extent dependent on fentanyl action. Considering the interquartile interval in the groups, we found that as early as at xenon concentration of 40 % in group 1, the percentage of δ-rhythm was 56.5 % (95 % CI: 53.5; 58.9) which corresponded to D2 level of hypnosis on the Kugler scale, while in group 2 it was 45 % (95 % CI: 38.5; 50.2) corresponding to the D1 level ($p < 0.001$). At 50 % xenon concentration, the percentage of δ-rhythm was 67.7 % (95 % CI: 65.7; 68.6) and the depth of general anesthesia corresponded to D2 in group 1 patients, while in group 2 it remained D1 (the δ-rhythm percentage was 53.7 % (95 % CI: 47.4; 58.4) ($p < 0.001$). Only at xenon concentration of 55 % or higher in patients of both groups, the depth of hypnosis according to Kugler classification reached D2 and the percentage of δ-rhythm was 69.2 % (95 %CI: 65.1; 73.6) in group 1 and 56.5 % (95 % CI: 49.6; 67.0) in group 2 ($p = 0.068$).

The use of fentanyl at an average dose of 0.39 ± 0.07 mg increased the proportion of δ-rhythm in the EEG spectrum by an average of 19.08 %, which corresponded to an estimated decrease in effective xenon concentration of approximately 20 %. When questioned using Brice questionnaire in the postoperative period, no episodes of awakening were registered in patients of both groups. We believe that this was due to the strict compliance with the study protocol, which ensured effective anesthesia and comprehensive patient monitoring, including that of clinical and instrumental data, when examining the effect of xenon concentrations on the depth of hypnosis.

Discussion

The main purpose of this study was to address the feasibility of assessing the true depth of hypnosis in elderly and senile patients and to determine the minimum safe concentration of anesthetic during xenon-induced anesthesia. This issue appears to be unresolved, especially in monoanesthesia with xenon, without the use of drugs affecting the level of consciousness and EEG. In the current literature, the studies assessing the depth of hypnosis during xenon anesthesia mostly have limitations related to age characteristics of the groups or to the use of drugs with a potentially sedative effect or those altering the bioelectric activity of the brain [15, 16]. The age characteristics of the patients in our study are very important. After all, the entire body, including the brain, undergoes physiological changes during aging, and EEG characteristics that differ in young and elderly patients such as reduced amplitude and power parameters, also change [17]. McGuigan S., comparing spectral characteristics of the EEG in patients undergoing general anesthesia with xenon and sevoflurane, noted that in xenon anesthesia the delta rhythm showed the greatest increase and leading role, the same trend we see in our study based on the EEG results. During sevoflurane anesthesia, along with delta rhythm, there was also an increase in alpha and theta rhythms [18]. During BIS-monitoring, which is widely used in clinical setting, a digital index is determined based on the archive data and frontal EEG without taking into account age aspects. This can lead to inaccurate estimation of consciousness level in elderly and senile patients, so one of our study objectives was to determine correlation between BIS-index values and the percentage of delta rhythm increase. Narcotic analgesics, often used for anesthesia during surgical intervention, have an unconditional influence on the depth of hypnosis. Their use can additionally increase this depth in elderly and senile patients considering the increased susceptibility of this group of patients to narcotics. Luginbuni M. reports that xenon use in orthopedic surgery does not reduce opioid use [19], but opioid use itself has depressing effect on the level of consciousness and EEG [20, 21]. Therefore, in our study we did not use narcotic analgesics in group 2 patients for the sake of accurate assessment of the true depth of hypnosis. The data on minimum alveolar concentration (MAC) for xenon in different studies vary from 63 to 71 % regardless of age. For example, in a paper by Goto T., published in Anesthesiology journal in 2001, the depth of hypnosis in xenon monoanesthesia was estimated in patients over 65 years old not using narcotics. The authors observed different levels of MAC in men (69 %) and women (51 %), however the level of hypnosis was estimated without EEG or other objective methods of brain activity assessment, by somatic response to skin incision at various concentrations of xenon [22]. Subsequently, a paper by Eger 2nd E. et al. appeared in the same journal, which challenged these findings, suggesting that xenon MAC value in women does not differ from men and recommending additional studies for further clarification [23]. The Kugler scale, which we used to determine the level of consciousness, is employed in the Narcotrend automatic analysis monitors. According to Stuttmann R., a strong correlation ($r = 0.957$) of monitor parameters during xenon anesthesia exists, but one of the study limitations was the use of remifentanil for pain control during anesthesia. The increased correlation could be due to a more smooth anesthesia profile with continuous narcotic infusion [12], in contrast to the “traditional” bolus scheme of narcotic administration “on demand” in group 1 in our study. Our EEG results have shown a higher percentage of increase in median delta rhythm in group 1 (by 19.08 % on average) *vs* group 2, with equal xenon concentrations in the groups (see Table 3). This intergroup difference was significant ($p < 0.001$) for xenon concentrations from 30 to 50 % and could be due to fentanyl administration intraoperatively at an average dose of 0.39 ± 0.07 mg. At the same time, the difference in BIS index values for both groups at anesthetic concentrations from 30 % to 60 % did not reach significance level ($p > 0.05$;

see Table 3), and the calculated Spearman rank correlation coefficient indicated that BIS monitoring in xenon monoanesthesia may be less accurate.

The study also aimed at establishing the effective concentrations of xenon based on EEG analysis for achieving the Kugler D2 level of hypnosis, providing an extremely low risk of awakening during anesthesia. This effective xenon concentration was 40% when fentanyl at a mean dose of 0.39 ± 0.07 mg was used and 55% for xenon monoanesthesia without narcotic analgesics. These data can be used in practice when working with xenon in order to prevent awakening during general anesthesia, as well as to avoid unnecessarily high drug concentrations.

Conclusion

In anesthesia with xenon combined with peripheral nerve blocks during knee arthroplasty in elderly and senile patients, a direct dependence of the EEG δ-rhythm activity increase on xenon concentration in the studied interval from 30 to 65% was observed. According to the Kugler scale, the increase in δ-rhythm percentage in the EEG spectrum over 50% corresponds to stage 11 (D2 depth of hypnosis), which suggests no episodes of awakening during general anesthesia. Such EEG changes were achieved in this cohort of patients at a xenon concentration of 55% in the group not using narcotic analgesics and at a concentration of 40% when bolus fentanyl was injected at an average dose of 0.39 ± 0.07 mg during anesthesia. The diminished correlation strength between δ-rhythm and BIS in the group without fentanyl and lack of significant difference in the bispectral index decrease between the groups may indicate a lesser diagnostic value of BIS-monitoring for accurate determination of the depth of hypnosis during xenon monoanesthesia.

Our study showed that the Kugler scale, as a simplified method of EEG analysis, can be used during xenon anesthesia to assess the depth of hypnosis, but the obtained data are more promising for validating methods of automatic interpretation of xenon-induced EEG changes.

Disclosure. The authors declare that they have no competing interests.

Ethics approval. The present study protocol was approved by the local Ethics Committee of the Institute for the Improvement of Physicians of the Pirogov National Medical and Surgical Center, Moscow, Russia (reference number: 11-26/11/2018).

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