EARLY ADMINISTRATION OF XENON-OXYGEN MIXTURE IN NEONATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY

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Hypoxic-ischemic encephalopathy remains a leading cause of neonatal mortality and disability. Experimental data suggest potential neuroprotective properties of xenon; however, the mechanisms and extent of its effect are not fully understood. The study aimed to evaluate the neuroprotective properties of a xenon-oxygen mixture in a neonatal ischemia-hypoxia rat model using MRI and follow-up neurological assessment. The experiment involved Wistar rat pups (n = 16). Neonatal ischemia-hypoxia was induced by the Rice–Vannucci method. Thirty minutes post-hypoxia, animals received the 60-min inhalation of either nitrogen-oxygen (control, n = 8), or 50/50 xenon-oxygen mixture (n = 8). Brain MRI was performed on day 7. In the xenon group, brain lesion volume was significantly reduced by 25% compared to controls on day 7 (p = 0.001). Neurological development was assessed from day 3 to 28 using a combination of behavioral tests. Xenon-treated animals demonstrated earlier formation of forelimb and hindlimb grasping reflexes (p = 0.025 and p = 0.005), better hindlimb placement and cliff avoidance on day 7 (p = 0.045 and p = 0.03), and better preserved auditory startle response on day 14 (p = 0.035). Thus, early administration of a xenon-oxygen mixture after ischemia-hypoxia exerts pronounced neuroprotection in newborn rats, confirmed by reduced brain damage and improved neurological outcomes.

Keywords: xenon, xenon-oxygen mixture, hypoxic-ischemic encephalopathy, neuroprotection, Rice–Vannucci model, rats

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Compliance with ethical standards: the study was approved by the Ethics Committee of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology (Protocol No. 2/25/5 dated March 26, 2025). All animal procedures were performed in accordance with the principles of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 1986). The report of the study was prepared in accordance with the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines.

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РАННЕЕ ПРИМЕНЕНИЕ КСЕНОН-КИСЛОРОДНОЙ СМЕСИ ПРИ НЕОНАТАЛЬНОЙ ГИПОКСИЧЕСКОЙ ИШЕМИЧЕСКОЙ ЭНЦЕФАЛОПАТИИ

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Гипоксическая ишемическая энцефалопатия остается одной из ведущих причин неонатальной смертности и инвалидизации. Экспериментальные данные свидетельствуют о потенциальных нейропротекторных свойствах ксенона, однако механизмы и выраженность его эффекта изучены недостаточно. Целью работы было оценить нейропротекторные свойства ксенон-кислородной смеси на модели неонатальной ишемии-гипоксии у крыс с использованием МРТ и динамического анализа неврологического статуса. Экспериментальная работа выполнена на крысятах линии Wistar (n = 16). Неонатальную ишемию-гипоксию моделировали по методу Райса–Ванучи. Через 30 мин после гипоксии животные получали ингаляцию либо азот-кислородной смеси (контроль, n = 8), либо ксенон-кислородной смеси 50/50 (n = 8) в течение 60 мин. На 7-е сутки проводили МРТ головного мозга. В группе ксенона объем повреждения головного мозга на 7-е сутки был статистически значимо ниже на 25% по сравнению с контролем (p = 0,001). Неврологическое развитие оценивали с третьих по 28-е сутки с использованием комплекса поведенческих тестов. Животные группы Xe демонстрировали более раннее формирование хватательных рефлексов передних и задних конечностей (p = 0,025 и p = 0,005), лучшую постановку задних конечностей и более выраженную реакцию избегания обрыва на 7-е сутки (p = 0,045 и p = 0,03), а также более сохранную слуховую стартл-реакцию на 14-е сутки (p = 0,035). Таким образом, раннее применение ксенон-кислородной смеси после моделирования ишемии-гипоксии оказывает выраженный нейропротекторный эффект у новорожденных крыс, что подтверждается уменьшением объема повреждения головного мозга и улучшением неврологических показателей.

Ключевые слова: ксенон, ксенон-кислородная смесь, гипоксическая ишемическая энцефалопатия, нейропротекция, модель Rice-Vannucci, крысы

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The term "hypoxic-ischemic encephalopathy" refers to acute damage to the brain structures caused by perinatal asphyxia. The prevalence worldwide varies between 1 and 3 cases per 1000 live births in developed economies, while in resource-limited States the prevalence can be 10 times higher [1, 2]. In the Russian Federation the rate is 13.3 per 1000 newborns [3].

The hypoxic-ischemic encephalopathy pathogenesis is induced by the cerebral perfusion decrease resulting in hypoxia, ischemia, and energy deficiency, and the neurological outcome severity is correlated with gestational age and localization of the lesion [4]. Oxidative stress, neuroinflammation, excitotoxicity, apoptosis, and cell necrosis represent the key links of the complex pathophysiological cascades induced in the brain. However, the exact pathophysiological mechanisms underlying the development of hypoxic-ischemic encephalopathy are poorly understood [5, 6].

Today, therapeutic hypothermia remains the only evidence-based neuroprotection method used in hypoxic-ischemic encephalopathy [7–10]. However, the method efficacy is limited, since therapeutic hypothermia only partially reduces the risk of mortality and disability [11–13]. This encourages active search for new therapeutic strategies capable of enhancing the effects of hypothermia or having independent neuroprotective effects.

One promising direction is the use of noble gases, which, according to experimental data, possess pharmacological activity [14–16]. Xenon is of particular interest, its neuroprotective properties have been demonstrated in various brain damage models [17]. However, the results of clinical trials, such as the international TOBY-Xe trial, have revealed no significant improvement of outcomes when adding xenon to hypothermia in full-term newborns [18, 19]. This does not mean that there is no xenon potential, but rather points to the need for more thorough preclinical assessment of the xenon mechanisms of action, dosing regimens, and delayed effects. In particular, the xenon ability to influence functional maturation of the brain in the post-ischemic period, which can be assessed in experimental models using the long-term neuro-behavioral testing and brain imaging methods, needs to be clarified.

The study aimed to evaluate the neuroprotective properties of a xenon-oxygen mixture in a neonatal ischemia-hypoxia rat model and assess the extent of brain damage and some neurological status indicators.

METHODS

The experiment involved male and female Wistar rat pups with the body weight of 25–30 g (n = 16). The animals were simply randomized into groups using a random number generator. Animals that showed signs of disease in the initial phase based on the results of a standard examination and behavior assessment were excluded from the study, along with the ones that died due to complications from anesthesia or surgical intervention. The following data were the criteria for humane withdrawal from the experiment: postoperative wound infection, no startle response, weight loss of more than 20% in one day, manifestations of autoaggressive behavior, inability to self-feed and drink 24 h after the ischemia-hypoxia induction.

The study design provided for formation of two experimental series. Control group (group C, n = 8): within 30 min after the ischemia-hypoxia modeling the animals were subjected to the nitrogen-oxygen mixture inhalation (nitrogen 50%/oxygen 50%; InertGasMedical, Russia) for 60 min. Experimental group (group Xe, n = 8): within 30 min after the ischemia-hypoxia modeling the animals received the xenon-oxygen mixture (XenOx 50, xenon 50% /oxygen 50%; registration certificate No. LP-006493, InertGasMedical, Russia) for 60 min. Laboratory animals were euthanized through the anesthetic agent overdose after the end of the experiment.

Neonatal ischemia-hypoxia was simulated using the Rice–Vannucci model [20]. Isoflurane anesthesia (induction 3%, maintenance 1.5–2% in 100% O_2) on the hot bench (36 °C) was used. The anesthesia depth was regulated by monitoring the loss of corneal and interdigital reflexes. After microsurgical isolation and lygation of the left common carotid artery we perceived no distal pulse, and the wound was sutured. The rat pups were placed in a thermostat (36 °C, 60 min), then in a multi-gas incubator with the hypoxic mixture (8% O_2 / 92% N_2) for 90 min with temperature monitoring and visual control.

Within 30 min after the end of hypoxia induction, during which the animals had access to the mother, the rat pups were placed in a chamber for 60 min for inhalation of the control and experimental gas mixtures. N_2/O_2 50/50 or XenOx 50 was supplied continuously with the flow rate of 0.5–1 L/min. The temperature within the chamber was regulated at 36°C, with the relative humidity maintained between 40% and 60%. There were no more than five rat pups in the chamber at once; a layer of wood litter was introduced at the base to ensure biological fluid absorption. The contour was fitted with a desiccant (silica gel) and CO_2 adsorber (soda lime); recirculation was ensured by a fan. The animals' arousal level and motor activity were assessed after the end of the exposure.

Neurological status

The newborn rat pups' neurological development was assessed using 8 behavioral tests starting from day 3 after birth in accordance with the previously reported protocols [21–23].

The forelimb grasping reflex was assessed starting from the third day of life: a blunt rod was gently pressed to the forelimb palmar surface, which normally induced finger flexion and grasp. The reflex was considered to be completely developed with stable grasping with both front paws throughout two consecutive days. A three-point assessment scale was used, where score 0 corresponded to no reflex, score 1 corresponded to grasping with one front paw (with the side specified), and score 2 corresponded to grasping with both front paws. Similarly, the hindlimb grasping reflex was assessed by the same method starting from the third day: score 0 — no grasp, score 1— grasping with one hind limb, score 2 — grasping with both hind limbs.

The righting reflex was also tested starting from the third day: the rat pup was placed in a supine position with the limbs straightened, and then released, recording the time taken to return to a prone position. The maximum time allowed for the response to complete was 15 s. No prone position restoration within this time was scored 0, roll over on the side (with the side specified) or incorrect posture was scored 1, and complete roll over resulting in a physiologically correct posture (onto all four paws) was scored 2.

The hindlimb placement reflex was assessed starting from the fourth day of life: the rat pup was held vertically by the body and the edge of a hard surface was touched with the back of the hind paw. Normally, the animal pulled back its paw and placed it on the surface. No response was scored 0, placement of one limb (with the side specified) was scored 1, and placement of both limbs was scored 2.

The cliff avoidance response also assessed starting from the fourth day was tested by placing the rat pup with its front paws and muzzle over the edge of a horizontal surface; a soft

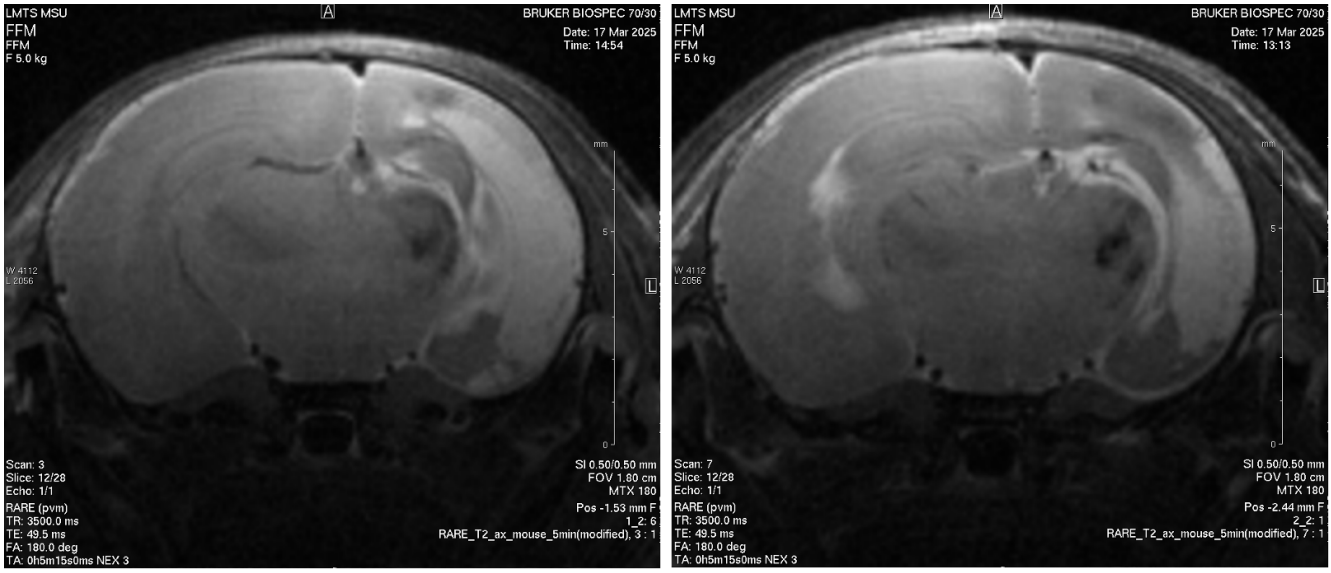

Fig. The animals' brain MRI scans on day 7. Group C — left, group Xe — right

pad was placed under the edge to prevent injury from fall. Reflexive avoidance manifested itself in turning away from the edge. No movement or fall was scored 0, an attempt to move away from the edge with dangling limbs was scored 1, and complete departure from the edge was scored 2.

The auditory startle response was assessed starting from the 10th day: a loud tone was presented just above the animal. Sudden movement or startle was considered as positive response and scored 1, no response was scored 0.

The nature of posture when moving on a non-slip surface was assessed starting from the 12th day of life. Not fully developed posture (dragging of the abdomen, the limbs perpendicular to the body) was scored 1, the fully developed posture (elevated abdomen, the limbs parallel) was scored 2; no movement corresponded to 0 points. At the same age, since day 12, eye opening was recorded: the eyelids fused shut corresponded to 0, opening of one eye (with the side specified) corresponded to 1 point, opening of both eyes corresponded to 2 points.

The limb sensorimotor function was assessed using the limb placement on support test. After three days of adaptation to hands the animals were through seven trials aimed at assessing the limb sensorimotor integration. The trials involved alternately moving the front and back paws off the edge of the table in different positions (with visual control, laterally, when pushing the body towards the edge, and when lowering to the surface by the tail). A three-point scale was used to assess performance in each trial: score 2 — normal performance, score 1 — slow or incomplete performance, score 0 — no response.

Magnetic resonance imaging

On day 7 after the ischemia-hypoxia modeling, the animals underwent *in vivo* MRI in the 7 T MRI scanner with the 105 mT/m gradient system (BioSpec 70/30; Bruker, Germany). After being anesthetized with isoflurane at a concentration of 1.5–2%, the animal was placed in a stereotactic fixation system with thermal control. A standard brain assessment protocol involving acquisition of T2-weighted images was used. A linear transmitter with the internal diameter of 72 mm was used to transmit the radio frequency signal; a surface receiver coil for the rat brain was used for signal detection. The RARE spin echo sequence had the following parameters: TR = 6000 ms, TE = 63.9 ms, slice thickness — 0.8 mm with an increment of 0.8 mm, matrix size — 256 × 384, resolution — 0.164 × 0.164 mm/pixel. The overall scan time per animal was about 30 min.

The extent of brain damage was assessed by planimetric analysis of MR images with subsequent calculation of the damaged tissue volume. The series of MRI scans was used to calculate the lesion area (mm^2) for each slice in ImageJ (National Institutes of Health, Bethesda, MD, USA). For that the areas of the intact tissue in the healthy (S_1) and damaged (S_2) hemispheres were isolated, and the lesion area for a slice was calculated using the following formula: $\Sigma S = S_1 - S_2$, where ΣS was the lesion area on a single slice (mm^2) [24]. The brain damage volume was calculated using the following formula: $V = \Sigma S_n \times d$, where d was the slice thickness (0.8 mm), ΣS_n was the sum of lesion areas on all slices (mm^2).

Statistical analysis

Statistical analysis was performed using SPSS Statistics 28.0.1 and GraphPad Prism 10.4.2. The distribution was tested for normality using the Shapiro–Wilk test. Since the indicators were ordinal scales and their distribution was non-normal, the data are provided as the median and interquartile range Me (Q_1; Q_3). Groups were compared using the Mann–Whitney *U*-test. The differences were considered significant with the two-tailed $p < 0.05$. To minimize the systematic error, the researcher, who conducted MRI and assessed the animals' neurological status in behavioral tests, was blinded; he/she was unaware of the rat pup distribution into groups.

RESULTS

According to the MRI imaging data obtained on day 7, the group of animals that received the xenon-oxygen mixture showed a significant brain damage volume reduction. This value was 25% lower, than in the control group ($p = 0.001$; Fig.).

The neurological status analysis revealed significant reflex formation acceleration in the rat pups of group Xe. On day 3, the median forelimb grasping reflex estimate of this group was significantly higher compared to that of the control group ($p = 0.025$; Table), which suggests a significant xenon-oxygen mixture neuroprotective effect in terms of motor functions. Similarly, even more pronounced dynamic changes were

Table. Neurological status indicators in rat pups of groups C and Xe

Day	Test	Group C (n = 8)	Group Xe (n = 8)	p-value
3	Forelimb grasping reflex	1 [0; 1]	1.5 [1; 2]	0.025
	Hindlimb grasping reflex	1 [1; 1]	1.5 [1; 2]	0.005
	Righting reflex	1 [0; 1]	1 [1; 2]	0.19
7	Hindlimb placement	0.5 [0; 1]	1.5 [1; 2]	0.045
	Cliff avoidance response	1 [0; 1]	1 [1; 2]	0.03
14	Startle response to tone	1 [0; 1]	1 [1; 2]	0.035
	Eye opening	1 [1; 2]	1 [1; 2]	0.1
28	Limb placement on support	12 [8; 13]	13 [12; 13.5]	0.08

reported for the hindlimb reflex (p = 0.005). The righting reflex test revealed no significant differences between the studied groups (p = 0.190).

On day 7, animals of group Xe showed significantly better performance in the hindlimb placement test (p = 0.045), as well as more pronounced cliff avoidance response compared to controls (p = 0.030).

By day 14, the significantly better preserved startle response to tone was reported in the rat pups, which received the xenon-oxygen mixture (p = 0.035). There were no significant differences in the terms of eye opening between groups (p = 0.100).

On day 28, sensorimotor integration assessment based on the limb placement on support test revealed no significant differences (p = 0.080).

DISCUSSION

The data obtained show that the xenon-oxygen mixture (50% Xe/50% O_2) inhalation in the early recovery period after ischemia-hypoxia has a pronounced neuroprotective effect in the Rice–Vannucci model rat model. A significant reduction of the brain lesion volume by 25% in the Xe group on day 7 based on the MRI data has become the key finding. This result is in line with the conclusions of the recent large-scale systematic review and meta-analysis showing that xenon reduced neurological deficit on average by 39.7% in mouse, rat, and swine pre-clinical hypoxic-ischemic encephalopathy models [25]. Our study confirms that even a single 60-minute application of xenon can significantly limit the development of brain infarction, as can be seen in T2-weighted images.

The improvement recorded in behavioral tests confirms morphological data and has a clear temporal logic. Improvement of grasping reflexes and the limb placement test results on days 3–7 suggests that xenon contributes to preservation of the sensorimotor pathways and cortical centers responsible for these reflexes. This is critically important since it is motor impairment that underlies such severe hypoxic-ischemic encephalopathy outcomes, as cerebral palsy. The preserved startle response to tone on day 14 suggests better functional state of the auditory systems and brainstem, which resonates with the data of the abovementioned review, in which the authors note the xenon capability of apoptosis reduction and neuroinflammation modulation [25]. The lack of significant differences in the limb placement on support test results on day 28 is likely to be associated with small sample size and high variability resulting from the immature brain's compensatory capacity.

Our findings fit well into modern concepts of the xenon mechanisms of action. The xenon neuroprotective effect is mediated by both NMDA receptor antagonism and pleiotropic effects: activation of two-pore-domain potassium channels, modulation of AMPA receptors, and, which is especially important for the neonate's brain, anti-apoptotic effect [26]. It has been shown that xenon reduces neuronal death and suppresses chronic neuroinflammation [27, 28]. Improvement of neurological outcomes in our experiment is likely to result from such a combined effect: limitation of primary lesion and creation of more favorable conditions for postnatal brain maturation.

Our preclinical data gain particular importance in the light of the results of clinical trials, such as TOBY-Xe. In this trial adding xenon to hypothermia in neonates did not result in improvement of outcomes, which the authors attribute, among other things, to the late start of therapy. In our study xenon was administered strictly 30 min after hypoxia, which emphasizes critical importance of the therapeutic window. According to other data, the maximum xenon efficacy is also achieved when therapy is initiated in the first hours after stroke [25].

Thus, the use of the xenon-oxygen mixture after modeling hypoxic-ischemic encephalopathy ensured neuroprotective effect in newborn rats, which allows us to consider the goal of the study as achieved. It is necessary to consider a number of limitations when interpreting the results obtained. The animal experiments did not involve therapeutic hypothermia being an essential component of modern clinical practice. Furthermore, the 28-day follow-up period is not equivalent to the complete life cycle, which leaves open the question of the long-term effectiveness of the drug.

CONCLUSIONS

The xenon-oxygen mixture (xenon 50%/oxygen 50%) administration in early neonatal ischemia-hypoxia ensures a pronounced neuroprotective effect in newborn Wistar rats, which is confirmed by significant brain lesion reduction by 25% on day 7 based on MRI data. The xenon-oxygen mixture contributes to acceleration of the central nervous system postnatal functional maturation: the earlier formation of grasping reflexes, improvement of sensorimotor responses, and preservation of auditory startle response have been reported in group Xe. The data obtained confirm the crucial role of early therapy initiation within the therapeutic window and substantiate the need for further exploration of optimal xenon dosing regimens, as well as xenon potential synergism with therapeutic hypothermia for optimization of hypoxic-ischemic encephalopathy treatment in newborns.

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