

Original Article

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Various Types of Xenon Anesthesia in Children

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In 2010-2011 with the permission of the Health Ministry of the Russian Federation A IIIA phase clinical trial research was held in order to assess the effectiveness and safety of xenon anesthesia in children (ASA I-III) with various surgical pathology. 60 xenon anesthesia were conducted among children aged from 1 to 18 years: Mask - 3 (5%), laryngeal mask - 9 (15%), and endotracheal - 48 (80%). Mask mono anesthesia with xenon has a lengthy induction; the circuit integrity is difficult to maintain, the gas flow is expensive; keeping in mind the described factors it has been defined as unpromising. The optimal xenon anesthesia is through a laryngeal mask or endotracheal. For all types of anesthesia premedication is necessary including 0.1% atropine sulfate. Induction in children younger than 5 years old should be carried out with sevoflurane via a face mask, and in children older than 5 years old with propofol. Analgesia at a 65-55% concentration of xenon in the anesthetic breathing mixture is inadequate and needs strengthening through the use of fentanyl intravenously.

Keywords: xenon, low flowed anesthesia, anesthesia in children.

More than a century has passed since the discovery of xenon (X). Nobel laureate William Ramsay (with J. Raleigh and M. Travers) has discovered four inert gases: argon, neon, krypton and xenon by using the method of spectral analysis from

1894 to 1898. In 1951 Americans C. Cullen and E. Gross (S. Cullen, E. Gross) conducted the first in the world xenon anesthesia, and 1951 was the start of using xenon anesthesia. However such anesthesia has not received rapid development due to complexity, high cost of obtaining gas and its large consumption during anesthesia. In the late 80s - early 90s in connection with the improvement of anesthesia and respiratory devices, the advent of high-quality gas analyzers and a wave of renewed interest in low flowed anesthesia has resumed interest in xenon [1, 2]. Being tolerant NMDA-receptor antagonist, it also has an impact on the GABA-receptors or not NMDA-glutamate ergo receptors, and kainate receptors [3]. Studies have shown that MAC X in the elderly depends on sex; it is lower for women about 51.1% and men - 69.3% [4]. In the clinic and auto experiment it was shown that the analgesic effect occurs within a few deep breaths of oxygen-xenon mixture at a concentration of $X/O_2 = 70\%/30\%$ [5-7]. In numerous studies of domestic and foreign authors positive hemodynamic effects of xenon as an anesthetic of choice in patients with compromising myocardial infarction [8, 9] has been convincingly shown. Recovery of cognitive function occurs early after anesthesia with xenon compared with isoflurane and sevoflurane anesthesia [10, 11]. In Russia the leading role in studying medical use of X belongs to national scientists headed by Professor N.E. Burov. Since 1991 the department of anesthesiology and resuscitation RMAPO has performed a full range of preclinical and clinical studies of xenon anesthesia in accordance with the requirements of Pharm Committee [7-10]. Order of the Health Minister of the Russian Federation from 08.10.1999 № 363 says that the Xenon is approved for medical use as means of anesthesia in adults in our country. Getting high purified xenon (99.9999%) allowed registering xenon under the brand name "XeMed." In 2010, the Health Ministry of the Russian Federation issued a permission (Order № 183 April 22, 2010) to conduct clinical studies of the gas as means of anesthesia in children located in SRI NDHIT (Moscow) and the Regional Children's Clinical Hospital № 1 (Yekaterinburg). In June 2011 a study assessing the efficacy and safety of general anesthesia in children with various surgical diseases has been completed and the results are presented in this paper.

Objective: To compare the different types of anesthesia with xenon during general anesthesia in children (ASA I-III) scheduled for surgery.

Patients and Methods

The clinical study included 60 children aged 1 to 18 years, 42 of whom were (70.0%) boys and 18 (30.0%) were girls admitted to the hospital for surgical treatment. Inclusion criteria were age under 18 years of age and physical status I-

III ASA. Class I had 18 (30.0%), Class II - 26 (43.3%) and class III - 16 (26.7%) patients. The exclusion criteria were: congenital and acquired heart and large vessels defects; patients requiring high oxygen concentration ($FiO_2 > 0,3$), emergency and outpatient surgeries.

Types of surgical procedures with xenon anesthesia are presented in Table A.

The greatest number of surgeries was performed in patients with abdominal pathology - 17 (28.3%), including Ivanisevich surgery, hernia repair (open and laparoscopic), cholecystectomy, Nissen stomach plication, the formation of choler jejune anastomosis by Roo etc. A smaller group with 13 (21, 7%) children consisted of the following: formation of pyelo ureter anastomosis, neo implantation of ureter, and nephrectomy. In children with neurosurgical pathology 13 (21.7%) operations such as: ventricular peritoneal shunt, crania plastic, vertebral column removal of dermoid cysts, etc. were performed. A small number of operations were carried out on the soft tissue defects (from injury) particularly plastic reconstructive in 7 (11.7%) cases. On the chest five (8.3%) operations were done involving correction of funnel-shaped keeled strain and removal of mediastina cysts, etc. Other section (at 5, 8.3%) included surgeries for removal of lymphangiom of various locations and hypospadias.

In order to perform the anesthesia, anesthesia-breathing apparatus (NDA) FELIX DUAL (TAEMA, France) and AXEOMA (Finland) designed to work with X were used. NDA SIESTA I Whispa (DAMECA, Denmark) was also engaged in the study, which was combined with the anesthetic attachment KNP-01 (JSC "Akela-N", Russia). Monitoring of gas ingredients was performed by using a mixture of gas analyzers: NDA, M1026V (Philips) and GKM-03-INSOVT (In/EtO₂, EtCO₂, In X and EtCO₂). Monitoring of vital functions was carried out by the watching system MR 60 (Philips) controlling blood pressure, the frequency of breathing, HR, SatO₂, BIS-index and index of perfusion. Clinical analyzes of blood were done by blood analyzer «Micros 60" (France), biochemical «Stat Fax» (USA); acid-base status of blood was controlled by «Radiometer Copenhagen ABL-500" (Denmark). Standard mathematical analysis and statistical processing were applied for evaluating results.

Results and discussion

The development of techniques using X for children was based on methods of xenon anesthesia in adult patients. The study used all known types of anesthetics used in pediatric anesthesia: Classical Mask (MA) anesthesia with a face mask, laryngeal mask (LMA), and endotracheal (ETA) anesthesia (Table 2). The use of

face masks was the smallest, in 3 (5%) cases with the average duration of MA was 44 ± 18 min. At the same time the consumption of xenon (445 ± 196 ml / kg / hour) appeared most costly in mask anesthesia. They were used for short operations in children with hernias of various locations. A large consumption of xenon at the MA was due to the inability to create "ideal" vacuum edge "apparatus-patient" versus LMA and the ETA, as well as the need to maintain the proper flow of breathing mixture to the child being at spontaneous breathing.

LMA was conducted in 9 (15%) children, lasting in average 56 ± 20 min. Consumption of xenon at LMA was 24% less than in MA and was 340 ± 120 ml / kg / h. At the same time, consumption of xenon at LMA was 29% greater than the ETA, which carried out the most traumatic and prolonged surgery. The average duration 48 (80%) ETA amounted to 114 ± 54 min with lower xenon expense 240 ± 80 ml / kg / h. The lowest gas loss at the ETA was due to tighter circuit in comparison with the MA and LMA as well as its duration. The longer the anesthesia, the lower the xenon expense in the equivalent of 1 hour.

Thus, the results of our studies on the consumption of xenon in children anesthesia coincide with the earlier results of research that had been conducted in adult patients. LMA and the ETA have the least expensive xenon consumption. In general anesthesia with xenon four periods were pointed out: 1 - the period of induction / de nitro genation, 2 - xenon saturation, 3 - maintenance of anesthesia, and 4 - awaking the patient.

Single Mask anesthesia with xenon

MA was carried out by using the apparatus FELIX DUAL (TAEMA, France). Before anesthesia, the child was selected the optimal size of the face mask to ensure a good vacuum circuit.

1. The induction period / denitrogenation with MA included only denitrogenation pursued by the flow of pure oxygen for more than 4 l / min (average of 6-8 l / min) for half-open circuit. Induction of xenon during this period was not conducted because it's not possible to create a necessary concentration of X without denitrogenation. The average duration of denitrogenation was 6 ± 1 min. The criterion for its completion was oxygen concentrations $\text{InO}_2 / \text{EtO}_2 = 98\% / 94\%$, determined by the gas analyzer.

2. The period of saturation was shaped along semi-enclosed circuit. The calculation of the flow of gaze narcotic mixture was 2 times higher than minute ventilation, and was not less than 3 liters / min. By setting the flow on the dosimeter apparatus at the concentration of gases in the ratio $\text{X} / \text{O}_2 = 70\% / 30\%$, not hermetical valve

of the apparatus was connected to the absorber to collect exhaled xenon for its subsequent processing. The average time of xenon saturation to the desired concentration in 60 - 67% (1.0 - 1.2 MAC) was 10 ± 3 min, after which the operation was begun. 1 (33.3%) out of the three children in a given period had an increased salivation, which required a sequence of actions such as depressurization of the breathing circuit, oropharynx cavity sanitation, double pressurizing of face mask and the resumption of xenon saturation. When the breathing system is depressurized, the concentration of anesthetic in the breathing mixture was quickly reduced, which required additional time and the amount of xenon in order to achieve the desired concentration (60-67%).

3. The period of maintenance of anesthesia was provided by the ratio of gases in the anesthesia breathing mixture, corresponding to $X/O_2 = 67-60\%/30\%$ gaze flow at least 3 liters / min. In this period of anesthesia flow of breathing gas was increased due to untighten mask fitting, which led to the unsealing of the contour and the decay of the breathing bag. All 3 (100%) children with single mask anesthesia with xenon in concentration 67-60% reported insufficient analgesia, which was manifested by an increase of breath, hypertension, tachycardia, and decreased perfusion index. Enhancement of analgesia was provided by fentanyl administration at a dose of 3 mg / kg resulting in a leveling of the negative symptoms and the successful completion of surgery and anesthesia.

4. At the period of awakening the patient' xenon flow was stopped, while increasing the flow of O_2 to 3.0 l / min 5 minutes before the end of surgery, usually during suturing of the skin. Upon reaching the xenon concentration in the circuit less than 15% the child opened his/her eyes and began to move the limbs. These manifestations corresponded to the value of BIS-index of more than 75 IU. Despite the small age of the patients, the period of awakening was "calm" and did not require further action in the form of anesthesia or sedation.

Thus premedication with atropine sulfate is necessary before induction of anesthesia during single mask anesthesia with xenon in children. During denitrogenization children react negatively to a tight fit of the face mask. Depressurization of the breathing system at any stage of anesthesia leads to a rapid awakening of the child due to rapid elimination of xenon caused by its physical characteristics (inert, fast inferred from the body). Single mask anesthesia with xenon concentration 67-60% (at the level of surgical anesthesia) does not provide adequate analgesia in children for planned surgery, which requires the use of fentanyl. The disadvantages of single mask anesthesia with xenon are: the duration of the induction period, the saturation of the X (20 min) and high consumption of

gas which unreasonably increases its cost. Given the above, single mask anesthesia with xenon in children has not been used further, and subsequent anesthesia in a study was conducted by using larynx mask or endotracheal intubation.

Endotracheal and Laryngeal mask xenon anesthesia

Techniques of LMA and ETA performed in routine surgical procedures were similar to each other, except for respiratory protection. In the first case it was a laryngeal mask, and the second - endotracheal tube. In adult patients and children in younger age group (under 5 years old) the induction of sevoflurane was used, and in older children (> 5 years) Diprivan was injected intravenously.

1. The induction period / denitrogenization. In children under 5 years old, the induction and introductory anesthesia with sevoflurane by inhalation "bolus" method were performed through a face mask on the half-open circuit with a gas flow 4-6-8 L / min (depending on the age of the child) 100% O₂. This method of induction has established itself as the "gold standard" for anesthesia in infants. The achievement and maintenance of anesthesia 3rd stage was 1-2 at induction with sevoflurane about 2 % (1MAK) allowing painless venous access of the child. At the same time BIS-index averaged 55 ± 5 U, corresponding to achieved stage of anesthesia. Following the venous access the flow of sevoflurane was stopped; intravenous sedation with atropine 0.01 mg / kg and then fentanyl in a dose of $2,9 \pm 1,1$ mg / kg were administered. Following this, in the case of anesthesia on spontaneous breathing, the installation was performed by laryngeal mask. In need for anesthesia in controlled breathing child muscle relaxant (esmerone at a dose of 0.6 mg / kg) was administered; laryngeal mask or intubation were performed by endotracheal tube, following by transfer to the ventilator.

In children older than 5 years old for the induction and introductory anesthesia short acting hypnotic (propofol) was used. It was injected slowly over 1.5 -2.0 min at a dose of $2,9 \pm 0,7$ mg / kg, following premedication with atropine. In accordance with BIS-index $44,7 \pm 11$ U, pre oxygenation was performed with 100% O₂; fentanyl was administered at a dosage of $2,9 \pm 1,1$ mg / kg; esmerone 0.6 mg / kg provided mioplegia, the installation of the laryngeal mask or tracheal intubation were made, followed by transfer of the child to artificial mechanical ventilation.

After respiratory protection denitrogenization was started by 100% O₂ flow 4 - 8 liters / min depending on the age of the child's half-open circuit. The average duration of de nitro genization was $6,2 \pm 1,0$ min. The criterion for its completion

were concentrations of oxygen on the inhale and exhale $\text{InO}_2/\text{EtO}_2 = 98\% / 94\%$, determined by the gas analyzer.

2. It's the period of xenon saturation. Immediately after the completion of denitrogenization saturation along a closed contour was started. A minimum flow of oxygen equaled to the metabolic needs of the body at the rate of $4\text{-}5 \text{ ml / kg / min}$ and the flow of anesthetic, which is equal $0,02\text{-}0,05\text{-}0,1$ (depending on age) until the ratio $\text{X/ O}_2 = 67 - 60\% / 30\%$ was established. The duration of xenon saturation was from 5 to 10 min ($7,5 \pm 1,8$) followed by the surgery.

3. There is a period of maintenance of anesthesia with xenon. Maintenance of anesthesia was carried out along the closed contour (closed system anesthesia). In order to support the minimum needs of the organism in the O_2 and to provide adequate anesthesia during surgery, it is necessary to maintain the concentration of the gas mixture in the circuit at a ratio of $\text{X: O}_2 = 67\text{-}60\% : 30\%$.

To ensure this relation and the concentration of gases in the anesthesia breathing mixture for closed system anesthesia, the flow of xenon should be $50,0 \pm 20 \text{ ml / min}$, which was based on the weight of the child consistent with the average height of $1,9 \pm 0,7 \text{ ml / kg / min}$, and the need for O_2 equaled to $4,6 \pm 1,9 \text{ ml / kg / min}$, which was higher compared with the values recommended in adult patients.

4. The period of patient awakening. For 5-10 minutes before the end of surgery admission of xenon in the breathing circuit NDA was stopped. Mechanical ventilation along a half closed circuit with a stream of oxygen $2\text{-}3 \text{ l / min}$ was continued. Exhaled xenon was trapped by the absorber unit. Closure of the skin was carried out at 50% xenon. Upon reaching the concentration of anesthetic in the contour at least 10-15% the children opened their eyes, beginning to respond to the endotracheal tube and moved limbs. Awakening after xenon anesthesia was quick, "comfortable" for the patient at any age; children woke up calmly with no needs for additional analgesia or sedation. Awakening from anesthesia with xenon distinguishes from all known anesthetic.

According to the result of intraoperative monitoring we have noted the lack of analgesic effect of single mask anesthesia with xenon (a mask method) when planning surgical interventions in children. This resulted an addition of analgesic component fentanyl. Fentanyl was administered in the induction of anesthesia and during the main phase of anesthesia which is presented in the Table 3.

Fentanyl doze applied during induction of anesthesia in different types of planned surgical procedures didn't differ from the total injected over the entire period of anesthesia, and averaged about 3 mg / kg . In thoracic surgery the total consumption of fentanyl was the lowest ($2,0 \pm 0,2 \text{ mg / kg / h}$), because xenon anesthesia

included epidural blockade. The need to introduce the stages of fentanyl anesthesia in each case was determined by the anesthesiologist on the basis of monitoring data and depended on the trauma of the surgery. Fentanyl was administered in presence of inadequate anesthesia: hypertension (blood pressure rise by 15-20% above baseline), decreased perfusion index (less than 1.0), and tachycardia (heart rate above 15-20% of baseline values). Vegetative response to nociceptive stimulation in children with xenon anesthesia in children younger than 5 years and older age varied. Children under 5 years old responded to pain in the forms of tachycardia, hypertension, and decreased perfusion index. The reaction of the older children in the nociceptive impulses manifested only as hypertension and decreased perfusion index, tachycardia wasn't noted.

The study analyzes the xenon consumption depending on the model of anesthetic apparatus (Table 4). Only laryngeal mask and endotracheal anesthesia were considered, the duration of which was more than 1 hour. The lowest flow rate of xenon in the period of saturation was detected in the NDA AXEOMA (Finland) - 129 ± 53 ml / kg. This flow rate was 6% lower than the saturation apparatus SIESTA I Whispa (DAMECA, Denmark) - 137 ± 58 ml / kg and 40% lower than the saturation FELIX DUAL (TAEMA, France) - 180 ± 65 ml / kg.

During maintenance of anesthesia with xenon, NDA AXEOMA (Finland) was the most economical equipment. Gas consumption at work was 179 ± 68 ml / kg / h, which is 6% lower than the SIESTA I Whispa (DAMECA, Denmark) - 189 ± 62 ml / kg / h and 13% less than when working at FELIX DUAL (TAEMA, France) - 202 ± 70 ml / kg / h.

Findings:

1. Single mask anesthesia with xenon via face mask in children is not promising; because the induction is long, maintenance of circuit integrity during anesthesia is difficult; and unnecessarily expensive gas consumption.
2. The optimal type of anesthesia with xenon is laryngeal mask or endotracheal anesthesia.
3. Prior to xenon anesthesia is appropriate to include premedication with atropine sulfate, 0.1%, and to enhance analgesia during induction of anesthesia and maintain it by fentanyl.
4. Induction in children younger than five years old by sevoflurane "bolus" method is recommended via a face mask on the half-open circuit, and in children older than 5 years via propofol.
5. The most money-saving xenon anesthesia machine is AXEOMA (Finland), compared with the SIESTA I Whispa (DAMECA, Denmark) and FELIX DUAL (TAEMA, France).

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Table 1: Types of surgeries

Types of surgeries	Number of surgeries (%)
Abdominal	17 (28,3)
Urological	13 (21,7)
Neurosurgical	13 (21,7)
Reconstructive-plastic	7 (11,7)
Thoracic	5 (8,3)
Others	5 (8,3)
Total	60 (100)

Table 2: The duration and the average consumption of xenon anesthesia at various ways

Type of anesthesia	Number (%)	The average duration of anesthesia (min)	The consumption of xenon (with saturation) (ml/kg/hour)
Mask	3 (5)	44±18	445±196
Laryngeal mask	9 (15)	56±20	340±120
Endotracheal	48 (80)	118±54	240±80

Table 3: Fentanyl Consumption during xenon anesthesia in children

Type of surgery	The stage of watery anesthesia (mkg/kg)	Total fentanyl consumption (mkg/kg/hour)
Abdominal and urological	3,0±1,2	3,5±1,5
Reconstructive-plastic	3,3±1,2	3,1±1,3
Neurosurgical	2,5±1,1	2,4±0,8
Thoracic*	3,0±0,5	2,0±0,2

Note: *When thoracic surgery was used xenon endotracheal anesthesia + epidural block

Table 4: Comparative analysis of xenon consumption depending on narcotic-breathing equipment

Narcotic equipment	The dose of xenon saturation (ml/kg)	Total xenon consumption (ml/kg/hour)
AXEOMA (Finland)	129±53	179±68
SIESTA I Whispa (DAMECA, Dania) + KNP-01 (Inc. «Ankela-N», Russia)	137±58	189±62
FELIX DUAL (TAEMA, France)	180±65	202± 70

Note: Laryngeal mask and endotracheal anesthesia longer than 1 hour were analyzed in xenon consumption