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Comparative study of the potentiating effect of isoflurane and sevoflurane on the duration of muscle relaxation during surgical interventions in one-day surgery in children

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Keypoints

To conduct a comparative assessment of the potentiating effect of modern inhalation anesthetics on the duration of muscle relaxants used in one-day surgery in children.

Abstract

The potentiating effect of various drugs used in anesthesiology, especially if this interaction is related to analgesic, hypnotic and muscle relaxant components, is always of interest for the development and implementation of new techniques of general anesthesia. Therefore, the purpose of our study was to carry out a comparative assessment of the potentiating effect of modern inhalation anesthetics on the duration of muscle relaxants used in one-day surgery in children. The study was conducted in AMU surgical clinics from 2010 to 2020. The study included 156 children aged 0 to 16 years of age at risk of I-II ASA anesthesia, who were operated on in a planned manner under combined general anesthesia. The study showed that atracurium besylate provided almost the same, with a high degree of predictability, the duration of deep neuromuscular blockade in children, regardless of age - which makes it the drug of choice for children in the first year of life. In cisatracurium besylate and rocuronium bromide, it was noted that the duration of deep neuromuscular blockade in children under 2 years of age is significantly longer than in older children. The shortest duration of action of rocuronium bromide was noted in children over 2 years of age when compared with atracurium and cisatracurium ($p < 0.01$). This fact makes it the main drug for providing myoplegia in children of this age with short-term surgical interventions.

Keywords

Sevoflurane, isoflurane, rocuronium bromide

Introduction

Recently, for a number of reasons, including economic ones, interest in inhalation anesthesia, which has long been the most widespread in the world, has been reviving. The potentiating effect of various drugs used in anesthesiology, especially if this interaction is related to analgesic, hypnotic and muscle relaxant components, is always of interest for the development and implementation of new techniques of general anesthesia. Especially, the muscle relaxant effect of modern inhalation anesthetics prompted us to conduct this study.

Aim of the study: to conduct a comparative assessment of the potentiating effect of modern inhalation anesthetics on the duration of muscle relaxants used in one-day surgery in children.

Material and Methods

The research was carried out in the surgical clinics of the AMU in the period from 2010 to 2020. The study included 156 children aged 0 to 16 years of age at risk of I-II ASA anesthesia, who were operated on in a planned manner under combined general anesthesia. In accordance with the requirements of the international program GCP (good clinical practice), all patients were included in the study only after receiving the voluntary consent of their parents. The criteria for excluding patients from the

study were the following conditions and history data that could affect neuromuscular transmission and safety:

- the use of antibiotics (except for penicillins and cephalosporins), lidocaine, quinidine, trimetaphan within the two preceding days before the start of anesthesia;
- planned use of corticosteroids for 1 month, monoamine oxidase inhibitors for two weeks, other antidepressants, anticonvulsants, antihistamines (H_1 receptor blockers);
- conditions predisposing to seizures, traumatic brain injury, hypoxic encephalopathy, cerebral edema, viral encephalitis;
- concomitant neuromuscular, neuropsychiatric or cardiovascular diseases, electrolyte disorders;
- conditions after extensive thermal damage;
- liver and kidney disease;
- history of bronchial asthma, if the patient received anti-asthma drugs within the last 6 months;
- malignant hyperthermia in the patient's history or in close relatives;
- history of inadequate response to muscle relaxant administration during previous operations.

During the study, all children were divided into 3 main groups depending on the muscle relaxant used:

IIIA (n = 52) - with the use of rocuronium bromide (esmeron), IIIB (n = 52) - with the use of atracurium besylate (trarium), IIIC (n = 52) - with the use of cisatracurium besylate (nimbex). Depending on the type of general anesthesia, these groups were divided into 2 subgroups: anesthesia based on isoflurane + fentanyl "+ iso", anesthesia based on sevoflurane + fentanyl "+ sev". Also, the main groups were subdivided into 2 age subgroups: children under 2 years of age – $IIIA_1$, $IIIB_1$, $IIIC_1$ and children from 2 to 16 years old – $IIIA_2$, $IIIB_2$, $IIIC_2$.

The distribution of the studied children, depending on the type of general anesthesia, is based on the concept of the potentiating effect of modern halogen-containing inhalation anesthetics on the duration of action of non-depolarizing muscle relaxants. Moreover, according to the literature, the degree of this influence is different (1, 2, 3, 4). Thus, isoflurane is able to prolong the duration of the action of muscle relaxants by 15-20%, and sevoflurane by 50-60% (5, 6, 7, 8, 9). The distribution of patients by type of surgery is presented in table 1.

Groups	disease (operation)	$IIIA_1$ ≤2 age	$IIIB_1$ ≤2 age	$IIIC_1$ ≤2 age	$IIIA_2$ >2 age	$IIIB_2$ >2 age	$IIIC_2$ >2 age
n=78 +iso	Cryptorchidism (laparoscopic orchiopexy)	1	1	1	2	1	2
	Varicocele (laparoscopic testicular vein ligation)	-	-	-	1	1	1
	Pyloric stenosis (pylorotomy)	1	1	1	-	-	-
	bilateral sided inguinal hernia (laparoscopic hernia repair)	5	5	5	2	2	2
	Teratomo of the lumbosacral region (removal of teratoma)	1	1	1	-	-	-
	Stage II-III adenoids. (adenoectomy)	-	-	-	1	1	1
	Chronic tonsillitis (tonsillectomy)	-	-	-	1	1	1
	Antromastoiditis (antromastoidectomy)	-	-	-	1	1	1
	Curvature of the nasal septum (septoplasty)	-	-	-	1	1	1
	Cholecystitis (laparoscopic cholecystectomy)	-	-	-	1	1	1
	Deafness (cochlear implant)	2	2	2	1	1	1
	Non-clogging of the hard palate	-	-	-	1	1	1
	Cheiloplasty	2	2	2	-	-	-
	Hydrocephalus (ventriculoperitoneal bypass grafting)	1	1	1	-	-	-
	Strabismus (elimination of strabismus)	-	-	-	1	1	1
n=78 +sev	Cryptorchidism (laparoscopic orchiopexy)	1	1	1	2	2	2
	Varicocele (laparoscopic testicular vein ligation)	-	-	-	1	1	1
	Pyloric stenosis (pylorotomy)	1	1	1	-	-	-
	bilateral sided inguinal hernia (laparoscopic hernia repair)	5	5	5	2	2	2
	Teratomo of the lumbosacral region (removal of teratoma)	1	1	1	-	-	-
	Stage II-III adenoids. (adenoectomy)	-	-	-	1	2	1
	Chronic tonsillitis (tonsillectomy)	-	-	-	1	1	1
	Antromastoiditis (antromastoidectomy)	-	-	-	1	1	1
	Curvature of the nasal septum (septoplasty)	-	-	-	1	1	1
	Cholecystitis (laparoscopic cholecystectomy)	-	-	-	1	1	1
	Deafness (cochlear implant)	2	2	2	1	1	1
	Non-clogging of the hard palate	-	-	-	1	1	1
	Cheiloplasty	2	2	2	-	-	-
	Hydrocephalus (ventriculoperitoneal bypass grafting)	1	1	1	-	-	-
	Strabismus (elimination of strabismus)	-	-	-	1	1	1
	Total 156	26	26	26	26	26	26

Table 1. Distribution of patients by the nature of surgery

All groups were comparable in terms of age and weight. The duration of anesthesia in different groups is shown in table 2.

Patient groups	Duration of surgery, min.	Duration of anesthesia, min.
IIIA + sev	147,5±3,3	157,7±5,8
IIIA + iso	148,6±3,5	168,6±4,5
IIIB + sev	150,3±4,4	163,3±5,9
IIIB + iso	150,1±4,5	170,1±6,5
IIIC+ sev	149,6±3,6	159,6±5,6
IIIC + iso	149,2±4,1	164,2±5,5

Table 2. Distribution of patients depending on the duration of surgery and anesthesia

The demographic characteristics of the different groups are shown in Tables 3-5.

Type of anesthesia	IIIA + iso (n=26)		IIIA + sev (n=26)	
Division into subgroups	$IIIA_1$ (< 2 age) (n=13)	$IIIA_2$ (> 2 age) (n=13)	$IIIA_1$ (< 2 age) (n=13)	$IIIA_2$ (>2 age) (n=13)
Age, years	0,82±0,03	8,52±0,12	0,94±0,03	8,63±0,13
Weight, kg	9,52±0,12	26,8±0,52	9,8±0,11	28,3±0,66
Gender, male/ female	9/5	8/5	7/5	9/4

Table 3. Demographic indicators of group IIIA (with rocuronium bromide)

Type of anesthesia	IIIB + iso (n=26)		IIIB + sev (n=26)	
Division into subgroups	$IIIB_1$ (<2 age) (n=13)	$IIIB_2$ (> 2ge) (n=13)	$IIIB_1$ (< 2 age) (n=13)	$IIIB_2$ (> 2 age) (n=13)
Age, years	0,91±0,04	7,56±0,15	0,82±0,04	8,72±0,16
Weight, kg	9,19±0,13	30,4±0,45	9,10±0,08	26,8±0,42
Gender, male/ female	8/7	7/6	6/5	8/5

Table 4. Demographic indicators of IIIB group (with atracurium b sylate)

Type of anesthesia	IIIC + iso (n=26)		IIIC + sev (n=26)	
Division into subgroups	$IIIC_1$ (< 2 age) (n=13)	$IIIC_2$ (> 2age) (n=13)	$IIIC_1$ (< 2 age) (n=13)	$IIIc_2$ (> 2age) (n=13)
Age, years	0,83±0,05	8,71±0,12	0,89±0,05	8,83±0,13
Weight, kg	9,11±0,11	28,7±0,53	8,82±0,06	29,5±0,37
Gender, male/ female	9/8	6/5	8/7	5/4

Table 5. Demographic indicators of group IIIC (with cisatracurium bsylate)

Body weight, age of patients, as well as the average duration of anesthesia and surgery in the study groups did not have statistically significant differences ($p > 0.05$). All children included in groups IIIA, IIIB and IIIC underwent general combined anesthesia using inhalation and non-inhalation anesthetics, narcotic analgesics, muscle relaxants and mechanical ventilation. For the purpose of premedication for all patients within 30 minutes. before the onset of anesthesia, midazolam was administered orally at the rate of 0.4 mg / kg, and atropine 0.01 mg / kg intravenously as needed. In children under 2 years of age, induction of anesthesia was performed with an inhalation anesthetic sevoflurane, and over 2 years old with a non-inhalation anesthetic propofol at a dose of 3.0-3.5 mg / kg. After the onset of narcotic sleep, 0.005% fentanyl was injected intravenously at the rate of 3 μg / kg, and then, 2-3 minutes later, one of the studied muscle relaxants in basic doses. Tracheal intubation was performed when a sufficient level of myoplegia (90% T_1 suppression according to TOF-Watch data) was achieved with the corresponding endotracheal tubes. Tidal volume was calculated using a Radford nomogram. Respiration rate corresponded to the age norm. All children underwent volume-controlled ventilation in IPPV mode with ventilation parameters maintaining PetCO2 at 35-40 mm Hg. with the standard method of performing operations, and 33-35 mm Hg. - with the laparoscopic method. Depending on the type and duration of surgery, after intubation, a probe was inserted into the stomach and the bladder was catheterized in all children. Maintenance of anesthesia in all patients was carried out under mechanical ventilation in

a semi-closed circuit with a gas flow from 3.0 to 6.0 l / min, depending on age. In the “+ iso” and “+ sev” subgroups, one of the inhalation anesthetics 1.0 MAC isoflurane and 1.3 MAC sevoflurane, respectively, was included in the gas narcotic mixture. Anesthesia was also maintained by fractional administration of 0.005% fentanyl at a dose of 1 μg / kg as needed. A constant level of myoplegia during the operation was provided only by bolus intravenous injections of maintenance doses of one of the studied muscle relaxants with T_1 recovery up to ≥10%. At the end of the surgery, tracheal extubation was performed in all studied patients in groups IIIA, IIIB and IIIC in the presence of adequate conditions determined by clinical signs and the data of the neuromuscular conduction monitor (T_1 recovery ≥75%, TOF ≥70%). Intraoperative infusion therapy was carried out with crystalloid solutions in volumes corresponding to the age and nature of surgical interventions. As a result of titration of the doses of muscle relaxants studied by us, the primary (main) and maintenance doses of muscle relaxants were determined, depending on the type of anesthesia (Table 6).

Type of general anesthesia	Rocuronium bromide, mg / kg	Atracurium besilate, mg / kg	Cisatracuria besylate, mg / kg
″+iso″	0,45/0,1	0,4/0,15	0,12/0,02
″+sev″	0,3/0,1	0,3/0,1	0,1/0,02

Table 6. Primary and maintenance doses of muscle relaxants depending on the type of anesthesia

Given the strong irritating effect of isoflurane on the upper respiratory tract, induction of anesthesia in the "+ iso" subgroup was carried out by intravenous administration of propofol at a rate of 3.0-3.5 mg / kg. After reaching the surface level of the surgical stage of anesthesia, they switched to maintaining anesthesia with isoflurane, with an exposure for 10 minutes. At the stage of tracheal intubation, after intravenous administration of 0.005% fentanyl 3 μg / kg, either rocuronium bromide was injected at a dose of 0.45 mg / kg, or atracurium besylate - 0.4 mg / kg, or cisatracurium besylate - 0.12 mg. Maintenance of anesthesia in all patients from the "+ iso" subgroup was carried out with 1MAC isoflurane. The maintenance doses of muscle relaxants in children of this group were 0.1 mg / kg for rocuronium bromide, 0.15 mg / kg for atracurium besylate, and 0.02 mg / kg for cisatracurium besylate. Isoflurane delivery was stopped when skin sutures were applied. In the “+ sev” subgroups, induction anesthesia was carried out only by inhalation in a semi-closed circuit with a gas flow of 2-6 l / min, depending on the age of the child. In all cases, stepwise induction was used, ranging from 0.6% to a maximum of 8 vol%. The exposure ranged from 2 to 5 minutes, after falling asleep completely, the concentration of sevoflurane in the inhaled mixture gradually decreased to the required level of 1.3 MAC on exhalation. After intravenous administration of 0.005% fentanyl at a dose of 2 μg / kg, rocuronium bromide was administered at a dose of 0.3 mg / kg, or atracurium besylate - 0.3 mg / kg, or cisatracurium besylate - 0.1 mg / kg. After reaching 90% T1 suppression, tracheal intubation was performed. Maintenance of anesthesia in all patients of this subgroup was carried out by 1,3 MAC with sevoflurane. The maintenance doses of muscle relaxants in children of this group were: rocuronium bromide - 0.1 mg / kg atracuria besylate - 0.1 mg / kg, cisatracuria besylate - 0.02 mg / kg. The delivery of sevoflurane, as in the case of isoflurane anesthesia, was stopped at the end of the operation.

Isoflurane is one of the most widely used inhalation anesthetics for maintaining general anesthesia in children. The ability of isoflurane to provide a sufficiently pronounced and reversible muscle relaxant effect was used by us to develop a technique for general anesthesia using low doses of muscle relaxants. We carried out a comparative assessment of neuromuscular block with titrated doses of rocuronium bromide, atracurium besylate, and cisatracurium besylate in combination with 1,3 MAC isoflurane (subgroup “+ iso”) at the stages of tracheal

intubation, maintenance of general anesthesia, and spontaneous restoration of neuromuscular conduction.

Induction of general anesthesia in children of this group was carried out by intravenous administration of propofol until the surgical stage was reached. After switching to anesthesia with isoflurane 1.3 MAC and subsequent intravenous administration of 0.005% fentanyl at a dose of 3 μg / kg and basic doses of rocuronium bromide 0.45 mg / kg (1.5xED95), atracurium besylate 0.4 mg / kg or cisatrcurium besilate - 0.12 mg / kg (2.5xED95).

Comparative dynamics of changes in T_1 and TOF indicators during the first 10 minutes after intravenous administration of the studied MR in children under 2 years of age are reflected in table 7.

Analyzing the data in the table 7, we can say that in young children the maximum rate of development of neuromuscular blockade differed in the group of rocuronium bromide at a dose of 0.45 mg / kg. Already after the first minute from the moment of administration, the average T_1 values were 38.9 ± 0.6% of the initial level, with the average TOF values being 39.1 ± 1.1%.

Due to the development of neuromuscular blockade, the decrease in muscle contraction in response to stimulation progressively increased in patients of this subgroup (Fig. 1). So, by the beginning of the 2nd minute, the maximum suppression of T_1 was 4.4 ± 0.6% of the initial data, with average TOF values - 14.1 ± 1.1%. In the subgroup with cisatracurium (IIIC) at a dose of 0.12 mg / kg, the lowest rate of depression of neuromuscular conduction was observed, where after 1 minute from the moment of administration, T_1 was still quite high and averaged 62.5 ± 0.6% from the initial level, with average TOF values - 64.5 ± 24.5%. The administration of the main dose of 0.4 mg / kg atracurium besylate in the IIIB subgroup ensured T_1 suppression in most patients by the end of the first minute - 56.1 ± 0.6% of the initial level, with mean TOF values - 63.0 ± 0.6% , which is less than that of rocuronium bromide. Further significant development of neuromuscular blockade also increased most progressively in the subgroup with rocuronium bromide (IIIA), where already at the 2nd minute most children had 90% suppression of T_1 on average 4.4 ± 0.6% of the initial level, with average values TOF - 14.1 ± 1.1%.

Time, min.	Indicators	IIIA$_1$ (with rocuronium bromide)	IIIB$_1$ (with atracurium besylate)	IIIC$_1$ (with cisatracurium besylate)
Initial data	T_1	100,4±0,5	100,3±1,1	100,1±0,6
	TOF	100,3±0,4	101,5±1,1	101,3±0,8
0	T_1	100,1±0,4	100,4±1,1	100,3±0,5 *
	TOF	102,4±0,4	102,8±1,1	102,6±0,7 *
1	T_1	38,9±0,6 *	56,1±0,6 *	62,5±0,6 *
	TOF	39,1±1,1 *	63,0±0,5 *	64,5±0,5 *
2	T_1	4,4±0,6 *	5,3±0,6 *	7,4±1,1 *
	TOF	14,1±1,1 *	17,7±1,1 *	20,9±1,1 *
3	T_1	1,5±0,5 *	8,6±0,5 *	1,7±0,4 *
	TOF	10,5±0,7 *	15,8±0,5 *	14,5±0,8 *
4	T_1	1,3±0,2 *	1,2±0,5 *	1,3±0,6 *
	TOF	6,5±0,5 *	9,8±5,5 *	10,8±7,1 *
5	T_1	1,4±0,4 *	1,3±0,4 *	1,4±0,4 *
	TOF	5,5±0,5 *	9,3±1,1 *	8,5±1,1 *
6	T_1	1,5±0,3 *	1,4±0,3 *	1,4±0,4 *
	TOF	5,3±0,6 *	9,0±1,1 *	6,7±1,1 *
7	T_1	1,5±0,3 *	1,2±0,5 *	1,2±0,4 *
	TOF	5,4±1,1 *	6,4±1,1 *	4,3±1,1 *
8	T_1	1,6±0,3 *	1,3±0,3 *	1,2±0,4 *
	TOF	5,5±0,5 *	7,2±1,0 *	6,2±1,1 *
9	T_1	1,6±0,4 *	1,3±0,4 *	1,2±0,4 *
	TOF	5,6±0,5 *	6,3±1,0 *	5,6±1,1 *
10	T_1	1,5±0,3 *	1,3±0,3 *	1,2±0,3 *
	TOF	5,6±0,3 *	6,6±1,0 *	5,3±1,1 *

Table 7. Dynamics of changes in T1 and TOF indicators during the first 10 minutes after the administration of loading doses of muscle relaxants in children under 2 years of age in the "+ iso" subgroup. Note: the statistical significance of the differences in indicators in relation to the initial data: * - p <0.001

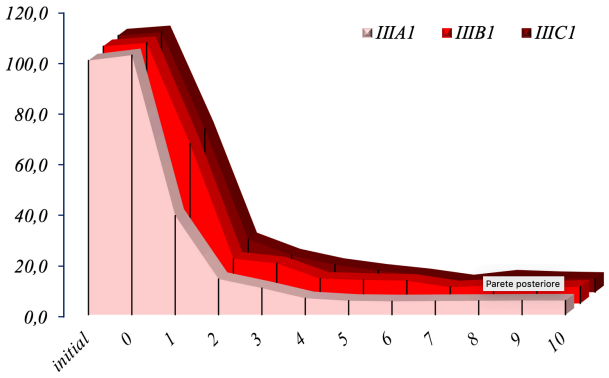

Figure 1. Dynamics of TOF changes during the first 10 minutes after the administration of loading doses of muscle relaxants in children under 2 years of age in the "+ iso" subgroup.

In the subgroup under 2 years of age in children with cisatracuria ($IIIC_1$), the mean values of T_1 and TOF were noted at levels of 7.4 ± 1.1% and 17.7 ± 1.1%, respectively, which also indicates a high efficacy of the drug and the development of neuromuscular blockade in the first 2 minutes from the moment of drug administration. Consequently, the necessary neuromuscular blockade during many surgical interventions in a larger percentage of children developed atracurium besilatam by the middle of the second minute, and cisatracurium besilatam only by the end of the second minute. The results of the study showed that, regardless of the type of muscle relaxant used, the maximum suppression of T_1 in children under 2 years of age is achieved faster than in children over 2 years of age.

Sevoflurane is the most commonly used inhalation anesthetic in pediatric anesthesiology. Fast and comfortable induction, a very high level of safety and a high elimination rate are the main criteria for choosing sevoflurane in multimodal combined anesthesia in children. In addition to direct action on the contractility of striated muscles, sevoflurane significantly enhances and prolongs the neuromuscular effects of non-depolarizing muscle relaxants, which can significantly reduce their dosage. In our work, we also studied the method of general anesthesia based on sevoflurane using low doses of rocuronium bromide, atracurium and cisatracurium besylate in various surgical interventions. Introductory anesthesia in all children of this group was performed with sevoflurane (+ sev) until the surgical stage was reached. After reaching the expiratory sevoflurane concentration of 1.3 MAC (according to the gas analyzer) and the subsequent administration of fentanyl at a dose of 3 μg / kg, the main doses of atracurium 0.3 mg / kg in group IIIB followed, cisatarcuria 0.1 mg / kg in the group IIIC and rocuronium bromide 0.3 mg / kg in group IIIA. The dynamics of the development of neuromuscular blockade within 10 minutes after intravenous administration of the main doses of the studied muscle relaxants are shown in table 8 and 9.

As can be seen from the data presented, in older age subgroups, the rate of development of maximum neuromuscular blockade was lower than in children under 2 years of age, and it took more time to achieve 95-100% T_1 suppression.

By the end of the 2nd minute from the moment of administration of muscle relaxants, the following were noted: in subgroup $IIIB_2$ - 27.3 ± 0.4% with TOF indices - 44.1 ± 1.1%; in subgroup $IIIC_2$ - 37.5 ± 0.5%, with TOF indices - 49.8 ± 1.1%; in subgroup $IIIA_2$ - 18.6 ± 0.5%, with TOF values - 32.9 ± 1.1%. At the 3rd minute from the moment of administration, only in the subgroup with rocuronium bromide, the majority of children developed the maximum neuromuscular blockade, where the mean T1 values were 5.6 ± 0.6%, with the mean TOF values being 16.5 ± 0.6%. In the atracurium and cisatracurium besylate subgroups, the maximum neuromuscular blockade in most children developed only during the 4th minute, where the T1 values were: in the $IIIB_2$ subgroup - 4.5 ± 0.5%, with average TOF values - 14.8 ± 0, 6%; in subgroup $IIIC_2$ - 6.6 ± 0.5%, with average TOF values – 18.1 ± 0.6%.

As a result, the highest, on average, rate of reaching the maximum suppression of T1 was noted in the subgroup of rocuronium bromide ($IIIA_2$) - 2.4 ± 0.5 minutes, compared with the subgroups of atracurium besylate (IIIB2) - 3.0 ± 1.3 minutes and cisatracuria besylate ($IIIC_2$) - 3.5 ± 0.8 min.

Time, min.	Indicators	IIIA$_1$ (with rocuronium bromide)	IIIB$_1$ (with atracurium besylate)	IIIC$_1$ (with cisatracurium besylate)
Initial data	T_1	102,0±0,5	102,5±0,4	101,6±0,5
	TOF	103,4±0,5	103,5±0,5	100,5±0,5
0	T_1	100,6±0,4	101,2±0,5	100,5±0,5
	TOF	101,4±0,4	103,6±0,4	103,7±0,4
1	T_1	58,2±0,6 *	64,8±0,6 *	67,3±0,6 *
	TOF	59,3±1,1 *	67,3±0,5 *	74,1±0,5 *
2	T_1	8,6±0,6 *	12,3±0,6 *	12,6±0,5 *
	TOF	17,1±1,1 *	25,4±1,1 *	27,8±0,9 *
3	T_1	5,8±0,5 *	8,7±0,5 *	8,8±0,8 *
	TOF	9,1±0,6 *	12,5±0,6 *	16,2±0,7 *
4	T_1	5,4±0,3 *	5,7±0,6 *	5,8±0,6 *
	TOF	7,6±0,5 *	10,5±0,5 *	11,5±1,1 *
5	T_1	3,1±0,4 *	6,6±0,5 *	5,3±0,5 *
	TOF	4,3±0,5 *	9,2±0,5 *	10,1±1,1 *
6	T_1	2,3±0,3 *	3,1±0,4 *	4,1±0,5 *
	TOF	4,8±0,6 *	8,1±0,5 *	8,6±0,7 *
7	T_1	2,2±0,3 *	3,7±0,3 *	3,9±0,4 *
	TOF	6,1±1,1 *	7,5±1,1 *	8,3±1,1 *
8	T_1	2,3±0,4 *	2,7±0,5 *	3,1±0,6 *
	TOF	4,5±0,6 *	7,8±0,6 *	7,5±0,6 *
9	T_1	2,8±0,4 *	2,5±0,5 *	3,5±1,0 *
	TOF	4,4±0,6 *	7,4±0,6 *	8,1±2,5 *
10	T_1	2,2±0,5 *	2,5±0,6 *	2,6±0,6 *
	TOF	6,5±1,1 *	8,3±0,5 *	8,1±0,8 *

Table 8. Dynamics of changes in T1 and TOF indicators during the first 10 minutes after the administration of loading doses of muscle relaxants in children under 2 years of age in the "+ sev" subgroup. Note: the statistical significance of the differences in indicators in relation to the initial data: * - p <0.001

Time, min	Indicators	IIIA$_2$ (with rocuronium bromide)	IIIB$_2$ (with atracurium besylate)	IIIC$_2$ (with cisatracurium besylate)
Initial data	T_1	101,4±0,5	101,5±0,6	103,3±0,5
	TOF	102,9±0,5	99,8±0,5	101,5±0,5
0	T_1	101,6±0,4	98,6±0,5	98,5±0,5
	TOF	101,7±0,4	101,3±0,4	100,3±0,5
1	T_1	58,6±0,6 *	65,6±0,6 *	67,2±0,6 *
	TOF	71,3±1,1 *	84,1±1,1 *	86,5±1,1 *
2	T_1	18,6±0,5 *	27,3±0,4 *	37,5±0,5 *
	TOF	32,9±1,1 *	44,1±1,1 *	49,8±1,1 *
3	T_1	5,6±0,6 *	9,4±0,4 *	10,3±0,5 *
	TOF	16,5±0,6 *	21,3±0,6 *	22,9±0,5 *
4	T_1	3,5±0,4 *	4,5±0,5 *	6,6±0,5 *
	TOF	12,5±0,6 *	14,8±0,6 *	18,1±0,6 *
5	T_1	2,3±0,4 *	2,2±0,5 *	2,4±0,3 *
	TOF	11,2±0,7 *	13,5±0,6 *	16,1±0,7 *
6	T_1	1,3±0,4 *	1,3±0,5 *	1,5±0,8 *
	TOF	10,9±0,5 *	11,5±0,6 *	15,7±0,6 *
7	T_1	1,3±0,3 *	1,4±0,5 *	1,4±0,5 *
	TOF	9,8±0,9 *	11,3±0,8 *	13,6±0,7 *
8	T_1	1,1±0,4 *	1,1±0,3 *	0,9±0,5 *
	TOF	6,2±0,3 *	8,3±0,5 *	8,4±0,3 *
9	T_1	2,4±0,3 *	0,6±0,2 *	0,7±0,3 *
	TOF	5,5±1,1 *	6,5±1,1 *	6,6±1,1 *
10	T_1	0,7±0,1 *	0,5±0,1 *	0,9±0,1 *
	TOF	5,2±1,1 *	5,3±1,1 *	7,2±1,1 *

Table 9. Dynamics of changes in T1 and TOF indices during the first 10 minutes after the administration of loading doses of muscle relaxants in children over 2 years of age in the "+ sev" subgroup. Note: the statistical significance of the differences in indicators in relation to the initial data: * - p <0.001

At the same time, the analysis of the study results showed that in all older age subgroups, the minimum time to achieve complete neuromuscular blockade, according to TOF-Watch, was noted in children aged 2 to 5 years (range from 1.8 minutes to 4.6 minutes) ... And the maximum is in children over 8 years old (range from 2.3 minutes to 5.3 minutes).

The maximum suppression of T_1 in all older age subgroups was also comparable and averaged 96 ± 2.7%, with a range from 95 to 100%.

When comparing the results obtained in this group with the "+ iso" group, where higher doses of the studied muscle relaxants were used, there was no statistically significant difference in time from the moment of administration to 10% T_1 recovery. This can be explained by the fact that the potentiating effect of sevoflurane is more powerful and manifests itself earlier than that of isoflurane, due to the lower blood / gas solubility coefficient (0.65 and 1.43, respectively), which ensures rapid equalization of its concentration in the alveolar air, in the blood and muscles, it was also found that the potentiating effect of sevoflurane in children is more pronounced in the subgroups using the benzylisoquinoline muscle relaxants atracurium and cisatracurium besylate compared with rocuronium bromide.

The results of the study showed that in order to provide short-term surgical interventions requiring tracheal intubation in children under 2 years of age, a single administration of atracurium besylate at a dose of 0.3 mg / kg is most expedient. And in children over 2 years of age, the optimal muscle-laxant is the use of rocuronium bromide at a dose of 0.3 mg / kg.

Summarizing the above, we can conclude that atracurium besylate provided almost the same, with a high degree of predictability, the duration of deep neuromuscular blockade in children, regardless of age - which makes it the drug of choice in children of the first year of life. In cisatracurium besylate and rocuronium bromide, it was noted that the duration of deep neuromuscular blockade in children under 2 years of age is significantly longer than in older children ($p < 0.001$). It should also be noted the shortest duration of action of rocuronium bromide in children over 2 years old, when compared with atracurium and cisatracurium ($p < 0.01$). This fact makes it the main drug for providing myoplegia in children of this age with short-term surgical interventions.

Conclusions

1. When isoflurane was included in the general anesthesia regimen, the main and maintenance doses of muscle relaxants were reduced and amounted to: atracuria besylate - 0.4 mg / kg and 0.15 mg / kg, cisatracuria besylate - 0.12 mg / kg and 0.02 mg / kg, rocuronium bromide - 0.45 mg / kg and 0.1 mg / kg.
2. When sevoflurane was included in the general anesthesia regimen, the main and maintenance doses of the studied muscle relaxants were reduced as follows: atracuria besylate - 0.3 mg / kg and 0.15 mg / kg, cisatracuria besylate - 0.1 mg / kg and 0.02 mg / kg, rocuronium bromide - 0.3 mg / kg and 0.1 mg / kg, respectively.

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