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A model of general anesthesia using modern muscle relaxants in one day surgery in children

E. M. Nasibova, R. Sh. Polukhov

Azerbaijan Medical University, Azerbaijan
Corresponding author: E. M. Nasibova, Azerbaijan Medical University. Email: doc.nasibova.esmira@gmail.com

Keypoints

To ensure comfortable working conditions for surgeons during laparoscopic operations in children over 2 years of age, the main doses of miorelaxants should be at least 0.4 mg / kg for atracuria, 0.12 mg / kg for cisatracurium and 0.45 mg / kg for rocuronium bromide.

Abstract

Introduction

In the last decade, there has been a widespread increase in interest in one-day surgery in children. The choice of the optimal model of anesthesia for minor surgery in children remains relevant to this day. 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.

Results and Conclusions

1. A decrease in the main and maintenance doses of non-depolarizing muscle relaxants rocuronium bromide, atracurium and cisatracurium besylate under conditions of combined anesthesia with 1.3 MAC of isoflurane provides excellent and good conditions for tracheal intubation, high-quality intraoperative relaxation, regardless of the methods of performing surgical interventions (traditionally or laparoscopically).
2. A single injection of 0.3 mg / kg rocuronium bromide, 0.3 mg / kg atracurium and 0.1 mg / kg cisatracurium besylate when combined with sevoflurane provide quality conditions for smooth tracheal intubation and mechanical ventilation in children of all age groups. The duration of the clinically effective action of the studied muscle relaxants in the indicated doses in children under 2 years of age makes it possible to provide high-quality relaxation during operations performed both traditionally and laparoscopically for 30-50 minutes. To ensure comfortable working conditions for surgeons during laparoscopic operations in children over 2 years of age, the main doses of miorelaxants should be at least 0.4 mg / kg for atracuria, 0.12 mg / kg for cisatracurium and 0.45 mg / kg for rocuronium bromide.

Keywords

Atracurium besylate, rocuronium bromide, cisatracurium besylate

Introduction

In the last decade, there has been a widespread increase in interest in one-day surgery in children. The choice of the optimal model of anesthesia for minor surgery in children remains relevant to this day. Neuromuscular

blockers (NMB) are important adjuvant to general anesthesia. Rocuronium bromide, atracurium besylate and cisatracurium besylate are considered relatively recently introduced non-depolarizing muscle relaxants (1,2,3,4,5,6,7,8,9,10). 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 (H1 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 (tracrium), ILC (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.

Table 1. Distribution of patients by the nature of surgery

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

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

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

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

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

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

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 4. Demographic indicators of IIIB group (with atracurium besylate)

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 5. Demographic indicators of group IIIC (with cisatracurium besylate)

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

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).

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

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

Results

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 into 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 besylate - 0.12 mg / kg (2.5xED95).

Comparative dynamics of changes in T1 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 Diagram1.

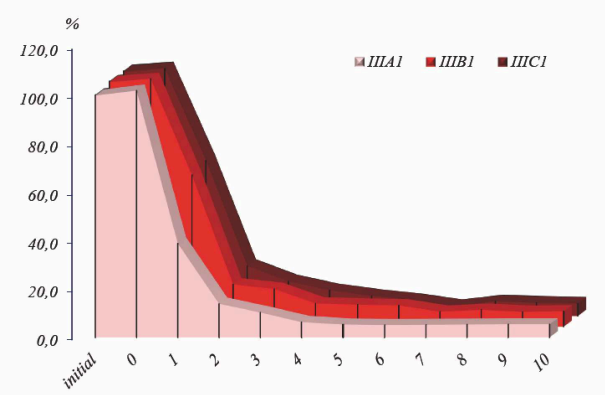

Diagram1. Dynamics of TOF change within the first 10 minutes after the administration of loading doses of muscle relaxants in children under 2 years of age in the "+ iso" subgroup.

By the beginning of the 2nd minute, the maximum T1 suppression was 4.4 ± 0.6% of the initial data, with average TOF values - 14.1 ± 1.1%. In the subgroup with cisatra-smoking (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, T1 was still quite high and averaged 62.5 ± 0.6% of the initial level, with average TOF values - 64.5 ± 24.5%. The introduction of the main dose of 0.4 mg / kg atracurium besylate in the IIIB subgroup ensured T1 suppression in most patients by the end of the first minute - 56.1 ± 0.6% of the initial level, with average TOF values - 63.0 ± 0.6%, which is less than 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 T1 on average 4.4 ± 0.6% of the initial level, with average TOF values - 14.1 ± 1.1%. By the second minute in the subgroup with atracurium (IIIB), the degree of suppression of the first muscle response T1 also approached 90% and averaged 5.3% ± 1.0%, with average TOF values - 17.7 ± 1.1%. In the subgroup under 2 years of age in children

with cisatracuria (IIIC1), the average values of T1 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.

In children over 2 years of age, the dynamics of the development of neuromuscular blockade during the first 2 minutes from the moment of administration had a similar picture with the younger age group, but was more extended in time (Diagram 2).

The development of neuromuscular blockade with the achievement of 90% suppression of T1 in children of the older age group occurred at the highest rate in the group with rocuronium bromide (IIIA2), so the mean values by the second minute were –19.6 ± 1.0%, TOF –35.7 ± 1.6%, by the beginning of the 3rd minute from the moment of administration it was –5.4 ± 0.1% with average TOF values –19.9 ± 0.8%. The dynamics of the development of the neuromuscular block at this stage in children of the older age groups IIIB2 and IIIC2 were somewhat different. Thus, by the 2nd minute in IIIB2 with atracurium besylate, the mean values of T1 and TOF were –22.9 ± 1.1% and 40.4 ± 1.3%, respectively..

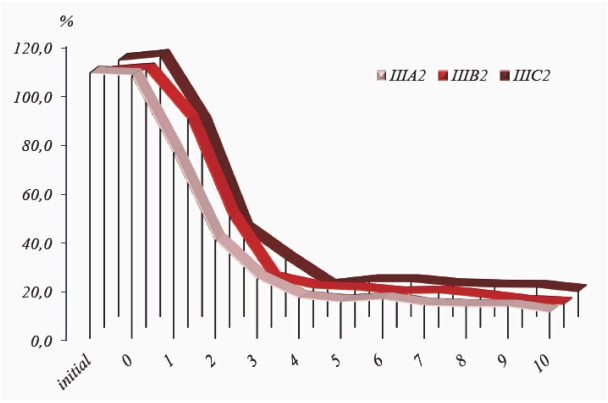

Diagram 2. Dynamics of TOF change within the first 10 minutes after the administration of loading doses of muscle relaxants in children over 2 years old in the "+ iso" subgroup.

The beginning of the 3rd minute from the moment of administration, according to TOF-Watch, was characterized by the rapid development of 90% neuromuscular blockade in IIIB2 and IIIC2 with average values of T1 and TOF: in subgroup IIIB2 - 7.9 ± 0.3% and 23, 6 ± 1.1%, and in subgroup IIIC2 - 8.4 ± 0.3% and 24.5 ± 0.9%, respectively

In our work, we also studied the method of endotracheal general anesthesia based on sevoflurane using low doses of rocuronium bromide, atracurium and cisatracurium besylate during 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 equal to 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 were administered in group IIIB, cisatarcuria 0.1 mg / kg in group IIIC and rocuronium bromide 0.3 mg / kg in group IIIA. The dynamics of the development of NMB within 10 minutes after the intravenous administration of the main doses of the studied muscle relaxanots are shown in diagram 3.

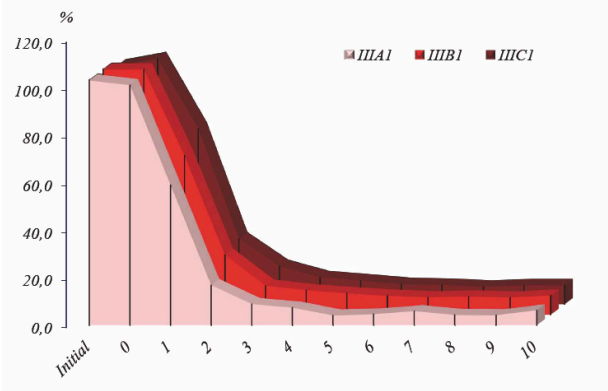

Diagram 3. Dynamics of TOF changes during the first 10 minutes after the administration of loading doses of muscle relaxants in children under 2 years of age in the "+ sev" subgroup

Analyzing the data of the first 2 minutes from the moment of administration, one can see that the average rate of T1 suppression in children under 2 years of age turned out to be comparable in all studied groups of muscle relaxants. However, some benefit of rocuronium bromide has been identified. By the end of 1 minute after the injection of rocuronium bromide at a dose of 0.3 mg / kg, according

to TOF-Watch, the mean T1 values in subgroup IIIA1 were 58.2 ± 0.6%, with the mean TOF values - 59.3 ± 1.1%. The degree of T1 suppression in other younger age subgroups at this point in time was somewhat different: in subgroup IIIB1 - 64.8 ± 0.6%, with mean TOF values –67.3 ± 0.5%, in subgroup IIIC1 –67 , 3 ± 0.6%, with average TOF values –74.1 ± 0.5%. Further, the development of NMB progressively increased, and by the end of the 2nd and the beginning of the 3rd minutes from the moment of administration of relaxants, 90% T1 suppression took place in all children of the younger age subgroup. At the same time, ro-kuronium bromide surpassed others in the rate of achieving the maximum NMB blockade. Thus, the average T1 values in the IIIA1 subgroup were 8.6 ± 0.6%, while the average TOF values were 17.1 ± 1.1%. In subgroups IIIB1 and IIIC1, the same indicators were: 12.3 ± 0.6% with mean TOF values –25.4 ± 1.1% and 12.6 ± 0.5% with TOF - 27.8 ± 0, 9% respectively.

As a result, the average time from the end of the administration of the primary dose of muscle relaxant to the development of the maximum NMB (suppression of T1 95-100%) in children under 2 years old was: in subgroup IIIA1 (rocuronium bromide) - 1.8 ± 0.3 min., in subgroup IIIB1 (atratcurium) - 2.0 ± 0.4 minutes, and in subgroup IIIC1 - 2.6 ± 0.6 minutes. The maximum suppression of T1 in all subgroups was comparable and averaged 9.7 ± 2.5% with a range from 97% to 99%.

As can be seen from Diagram 4, in older age subgroups, the rate of development of the maximum NMB was lower than in children under 2 years of age, and it took more time to achieve T1 suppression of 95-100%. By the end of the 2nd minute from the moment of administration of muscle relaxants, the following were noted: in subgroup IIIB2 - 27.3 ± 0.4% with TOF indices - 44.1 ± 1.1%; in subgroup IIIC2 - 37.5 ± 0.5%, with TOF indices - 49.8 ± 1.1%; in subgroup IIIA2 - 18.6 ± 0.5%, with TOF values - 32.9 ± 1.1%. In the period of 3 minutes from the moment of administration, only in the subgroup with rocuronium bromide, most children developed the maximum NMB, where the mean T1 values were 5.6 ± 0.6% with the mean TOF values - 16.5 ± 0.6% ... In the atracurium and cisatracurium besylate subgroups, the maximum NMB in most children developed only during the 4th minute, where the T1 values were: in the IIIB2 subgroup - 4.5 ± 0.5%, with average TOF values - 14.8 ± 0, 6%; in subgroup IIIC2 - 6.6 ± 0.5%, with average TOF values – 18.1 ± 0.6%.

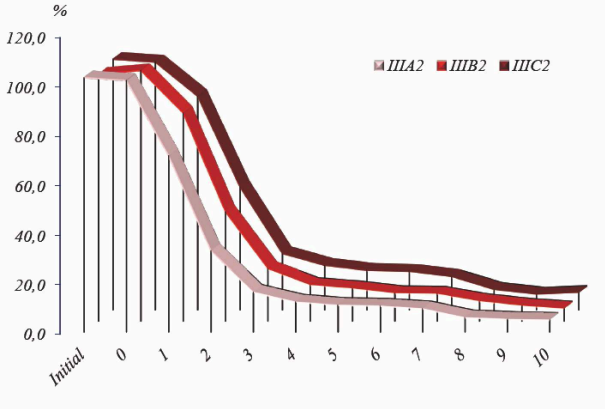

Diagram 4. Dynamics of TOF changes during the first 10 minutes after the administration of loading doses of muscle relaxants in children over 2 years of age in the "+ sev" subgroup.

As a result, the highest, on average, rate of reaching the maximum suppression of T1 was noted in the subgroup of rocuronium bromide (IIIA2) - 2.4 ± 0.5 minutes, compared with the subgroups of atracurium besylate (IIIB2) - 3.0 ± 1, 3 min. and cisatra curia besylate (IIIC2) - 3.5 ± 0.8 min. At the same time, the analysis of the study results showed that in all older age subgroups, the minimum time to reach full BMI, 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).

Conclusion

1. A decrease in the main and maintenance doses of non-depolarizing muscle relaxants rocuronium bromide, atracurium and cisatracurium besylate under conditions of combined anesthesia with 1.3 MAC of isoflurane provides excellent and good conditions for tracheal intubation, high-quality intraoperative relaxation, regardless of the methods of performing surgical interventions (traditionally or laparoscopically).

2.A single injection of 0.3 mg / kg rocuronium bromide, 0.3 mg / kg atracurium and 0.1 mg / kg cisatracurium besylate when combined with sevoflurane provide quality conditions for smooth tracheal intubation and mechanical ventilation in children of all age groups. The duration of the clinically effective action of the studied muscle relaxants in the indicated doses in children under 2 years of age makes it possible to provide high-quality relaxation during operations performed both traditionally and laparoscopically for 30-50 minutes. To ensure comfortable working conditions for surgeons during laparoscopic operations in children over 2 years of age, the main doses of miorelaksants should be at least 0.4 mg / kg for atracuria, 0.12 mg / kg for cisatrakuria and 0.45 mg / kg for rocuronium bromide.

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