



Research paper

Comparison of mivacurium and rocuronium in the microsurgery of the larynx

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ABSTRACT

Introduction: The introduction of sugammadex has created new opportunities for a quick reversal of relaxation caused by steroid relaxants.

Aim: The objective of this study was to compare relaxation of striated muscles in laryngeal microsurgery depending on the applied agent: mivacurium or rocuronium.

Material and methods: 65 low-risk surgery patients were randomly divided into two groups: MIV ($n = 32$) and ESM ($n = 33$) before the scheduled larynx microsurgery. The MIV group used mivacurium to relax the muscles, the ESM group used rocuronium. The following parameters were monitored: pulse rate, arterial blood pressure, arterial blood saturation, ventilation parameters according to the conventional standards and the depth and rate of neuromuscular blockade (NMB) reversal. The demand for anesthetics and analgesics used during the anesthesia and the frequency of complication occurrence were evaluated.

Results and discussion: There were no differences under intubation conditions. The conditions of the operation assessed by its operator were better in the ESM group. The time of the operation was similar in the two groups. The acting time of sugammadex in the ESM group was on average 1 minute. The ESM group reached train-of-four ratio (TOFR) of 0.9 (90% recovery of NMB) far more quickly than the MIV group. There was no statistical difference in side effects.

Conclusions: It seems to be reasonable to replace mivacurium with rocuronium and reverse its action by means of sugammadex in patients with a positive family history of allergy and anesthetized for short-term operations or operations of unpredictable duration.

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1. INTRODUCTION

Laryngologists employ microsurgery of the larynx in order to diagnose and treat patients. It is a procedure whose duration is difficult to estimate, and at the same time, it requires full relaxation of striated muscles.¹ A typical operation lasts about 15–30 minutes, and routinely a short-acting muscle relaxant is used, that is mivacurium. Unfortunately, this drug has a number of side effects, among which allergic response is most common. This precludes applying mivacurium in patients with positive history of allergy and bronchial asthma.² For such patients rocuronium is an alternative, yet because of its intermediate acting time, a complete reversal of neuromuscular blockade (NMB), caused by this agent is necessary in order to promptly awaken the patients from anesthesia. The introduction of sugammadex has created new opportunities for a quick reversal of relaxation caused by steroid relaxants, which include rocuronium. Sugammadex has provided anesthesiologists with a previously unknown opportunity to reverse muscular relaxation caused by steroid relaxants, such as rocuronium.³

2. AIM

The objective of the study was to compare relaxation of skeletal striated muscles in laryngeal microsurgery depending on the relaxant applied: mivacurium or rocuronium, in terms of the rate of acting, the quality of NMB the rate of reversal of NMB, the conditions of intubation and side effects.

3. MATERIAL AND METHODS

The prospective study included patients between 18 and 65 years of age in risk group I and II according to the American Society of Anesthesiologists (ASA) and for whom the BMI did not exceed 30 kg/m². The patients were qualified if their body temperature was normal (between 36.5°C and 37.1°C), as skin temperature influences its resistance and electrical conductivity. The minimal skin temperature should be

35°C. Lowering temperature by 1°C causes an increase in the value of one impulse by 15%, that is why the patients qualified for the study had to have normal temperature.³

The study did not include obese patients whose intubation was predicted to cause problems (on the basis of patient history, a routine clinical examination and the Mallampati score⁴), as well as patients below 18 and above 65 years of age, patients with history of allergies, including allergy to any agents planned to be used during the study, asthmatic patients, patients with disorders of kidneys and/or liver. Also patients on any medication which might cause interactions with relaxants, as well as patients with neuromuscular disorders and previously diagnosed enzymatic defects were disqualified. The analyzed groups did not differ between each other when it comes to demographic data, hemodynamic parameters, as well as arterial blood saturation before and during the operation (Table 1). Demand for remifentanyl and propofol was the same in both groups.

The study group consisted of 65 low-surgical-risk patients, randomly divided into two groups: MIV ($n = 32$) and ESM ($n = 33$) before the scheduled larynx microsurgery. All of the patients were anaesthetized by means of the TIVA method using propofol and remifentanyl. The MIV group received mivacurium to relax the muscles, the ESM group received rocuronium. After the operation, in the MIV group a spontaneous recovery of NM transmission was expected, whereas in the ESM group sugammadex was administered. The following parameters were monitored: pulse rate, arterial blood pressure, arterial blood saturation, ventilation parameters according to the conventional standards, and the depth and rate of NMB reversal (by means of TOF-Watch SX and the Krieg scale⁵). The following times were monitored: T1-TOF = 0, T2-TOF = 1, T3 – the end of the operation, T4 – the application of sugammadex, T5-TOFR = 0.9, T6 – the patient's extubation, (TOF interpretation: a presence of 4th twitch = 0%–5% paralysis, 3rd twitch = 65%–75% paralysis, 2nd twitch = 85% paralysis, 1st twitch = 95% paralysis, 0 twitch = 100% paralysis, TOFR = 0.9-T 90% recovery of NMB).

The demand for remifentanyl during anesthesia and the frequency of complications occurrence were evaluated.

Table 1. The characteristics of the analyzed groups.

Parameter	MIV group, mean ± SD	ESM group, mean ± SD	<i>P</i>
Age, years	53.09 ± 9.46	50.30 ± 9.38	0.16
Height, m	1.69 ± 0.06	1.70 ± 0.09	0.69
Body mass, kg	70.56 ± 10.90	70.88 ± 13.81	0.23
BMI, kg/m ²	24.40 ± 3.10	24.16 ± 3.25	0.76

Comments: MIV group consisted of 32 patients, ESM group consisted of 33 patients.

Table 2. Krieg scale: intubating and operating conditions: 3–4 score – perfect, 5–7 score – good, 8–10 score – imperfect, 11–12 score – bad.⁵

Score	1	2	3	4
Laryngoscopy	easy	good	difficulte	impossible
Vocal cords	open	moving	contacting	closed
Cough reflex	none	movement of the diaphragm	weak	strong

The study was eventually completed with 32 patients in the MIV group and 33 patients in the ESM group. Three patients were excluded from the MIV group at the stage of applying anesthesia: 1 because of unforeseen difficulties with intubation, and 2 because of improper function of the TOF-Watch. Two patients were excluded from the ESM group at the same stage: 1 because of prolonged operation and the need to use a surgical laser, 1 because of incorrect calibration of the TOF-Watch.

The characteristics of the study group were presented for the quantitative variables by means of the following parameters: the number of patients (n), the mean value (mean), standard deviation (SD), minimum and maximum values of the variable. When it comes to qualitative variables, the numbers (n) and percentages of population in the analyzed groups were given. The normality of quantitative variables distribution was evaluated with the visual method, parameters of skewness and kurtosis and the Shapiro–Wilk normality test. In order to compare qualitative variables in the analyzed groups who received mivacurium and rocuronium, the χ^2 test was used. When the expected numbers in at least one subgroup were lower or equal 5, Fisher's exact test was applied. Student's t -distribution test was used for quantitative variables of normal distribution and equal variances in order to compare differences in mean values of the analyzed features between independent groups. For variables of distributions other than normal, a non-parametric equivalent of t -distribution was used – the Mann-Whitney U test. Research hypotheses assuming homogeneity of variance between the compared groups were verified with Levene's test. Calculations were done in SPSS Statistics v. 17.0 software. Changes in time were analyzed with

ANOVA. For variables which did not meet the assumption of normality of distribution, a non-parametric equivalent of ANOVA test was used – the Kruskal-Wallis test. In all analyses a significance level of $P = 0.05$ was assumed. Differences at P less than 0.05 were seen as statistically significant.

4. RESULTS

No differences in intubation conditions between the groups were found on the basis of the Mallampati score and the Krieg scale, which is presented in Table 3.

Surgical conditions for performing the operation assessed in its 10th minute proved better in the ESM group, which is presented in Table 4.

The ESM group achieved TOF = 0 significantly faster, while the MIV group significantly faster achieved TOF = 1. The time of completing the surgical procedure was similar for both groups. The ESM group reached TOFR = 0.9 significantly faster than the MIV group (Table 5).

No statistically significant difference was observed in the frequency of complications in both groups, which is presented in Table 6.

5. DISCUSSION

There are a few methods to anesthetize patients in microsurgery of the larynx. According to Kleinsasser, believed to be the founder of intralaryngeal microsurgery, the best and

Table 3. Intubation conditions evaluated on the basis of the Mallampati score and the Krieg scale.

Intubation conditions	MIV group, mean \pm SD	ESM group, mean \pm SD	P
Krieg scale	3.41 \pm 0.56	3.67 \pm 0.69	0.11
Mallampati score	1.47 \pm 0.50	1.52 \pm 0.50	0.71

Table 4. Surgical conditions for performing the procedure assessed in the 10th minute after applying anesthesia with the use of the Krieg scale.

Surgical conditions	MIV group, mean \pm SD	ESM group, mean \pm SD	P
Krieg scale	4.06 \pm 0.87	3.58 \pm 0.50	0.01

Table 5. Monitored times: T_1 (TOF = 0), T_2 (TOF = 1), T_3 – the end of the operation, T_4 – the application of sugammadex, T_5 – TOFR = 0.9, T_6 – the patient's extubation.

Grup	T_1 mean(min)	P	T_2 mean(min)	P	T_3 mean(min)	P	T_4 mean(min)	T_5 mean(min)	P	T_6 mean(min)	P
MIV	2.62	0.002	15.10	0.002	19.45	0.26	none	28.32	0.009	29.51	0.07
ESM	2.01		19.38		21.77		22.72	23.83		26.36	

Table 6. Comparison of complications and unwanted effects observed during the study.

Side effects	MIV group	ESM group
Skin redness in the face and neck	1	0
Rash	2	0
Bronchospasm	1	0
Prolonged NMB	1	0
Bradycardia	0	1

simplest method for almost all patients consists in endotracheal anesthesia or intravenous anesthesia with the use of intubation tube with a small-diameter collar.¹ No matter which method is applied, anesthesia should fulfil two main objectives: to make it possible to perform the procedure in a manner which is painless and safe for the patient, and to provide the operator with comfortable working conditions.³

In the analyzed groups, lesions appeared mainly in the anterior commissure of the larynx and in the glottis on the vocal cords and in the supraglottis.

The first time determined during anesthetizing patients is the time to achieve TOF = 0 (T1). This time proved significantly shorter in the ESM group, which results from the properties of rocuronium, which is at the moment the only fast-acting non-depolarizing drug. The intubation dose of 0.6 mg/kg of bodyweight made it possible to achieve intubation conditions on average in 2 minutes. Numerous data in the literature confirm that comfortable intubation conditions are achieved after this dose of rocuronium in 60–120 s, yet this does not mean that all four responses disappear in TOF. Wright et al. published a very interesting paper, having compared the response from laryngeal adductor with the response of adductor pollicis muscle after rocuronium and succinylcholine.⁶ It appeared that laryngeal adductors are more resistant to rocuronium than adductor pollicis muscles. It can transpire clinically in a contraction of vocal folds during intubation, although TOF is 0. In this study, no such response was observed in the ESM group, while in the MIV group it occurred in 4 patients, in 2 of them additionally diaphragm movements were observed during intubation. In the ESM group, diaphragm movements were observed in 2 patients, although TOF was 0. No response in TOF to neural stimulation does not exclude the possibility of diaphragm movements. It is commonly known that as a result of activity of relaxant agents, relaxation encompasses subsequent muscle groups, starting from extraocular muscles, facial and pharyngeal muscles, limb muscles, abdominal wall muscles, and finally – the diaphragm. In one of the studies evaluating the relationship between TOFR and clinically confirmed residual relaxation, it was determined that there is a considerable individual changeability in the case of applying mivacurium. Among 12 volunteering patients, all were able to stick out their tongues, no matter what TOFR was. One of the subjects were not able to clench their teeth at TOFR = 0.84, while four of them clenched their teeth below TOFR = 0.4.⁷ In the group in which mivacurium was administered, good intubation conditions were achieved after 2.6 minutes on average, which is comparable with numerous reports in the literature.^{2,8,9} Diefenbach et al. reached 2.5 minutes for intubation after administering mivacurium doses equal 2–3x ED.¹⁰

In order to intubate patients a 5 mm intubation tube was used to provide favorable conditions to look into the larynx and perform the procedure. Intubation conditions were clinically assessed with the Krieg scale during the operation and the Mallampati score before the operation. In both analyzed groups they were similar, and were regarded as good

or very good. The same results were achieved by Pendeville et al., when they compared intubation conditions for mivacurium and rocuronium in one-day surgery procedures.¹¹ Their criterion to assess intubation conditions consisted in easiness to perform laryngoscopy, the position of vocal folds, response from airways and limb movements.

Patients who were expected to cause problems while being intubated were disqualified from the study at the stage of anesthesiological consultation.

Surgical conditions for the operation were assessed by the operators in its 10th minute on the basis of the Krieg scale; they differed between the analyzed groups. Although they were considerably better in the ESM group, the operation in the MIV group did not last longer than in the ESM group.

When the operation was complete, infusion of anesthetics was discontinued and sugammadex was administered in the ESM group in order to reverse NMB. Although the effect of mivacurium can also be reversed with the use of AchE inhibitors, practically speaking with neostigmine, there is a risk of strengthening NMB, thus this way is not commonly used. As it is known, mivacurium is broken down by plasma cholinesterase, so administering its inhibitor could lengthen the activity of mivacurium. Sugammadex was on average administered in the 23rd minute of the anesthesia (T₄). Most of the ESM patients were then in the phase of surgical relaxation in which TOF was 1 or 2. Thus the administered dose of sugammadex was 2 mg/kg of body weight. Ten patients remained in the phase of deep anesthesia, with TOF = 0; in those patients posttetanic count was determined, and it was more than 1 in all cases. So there was no threat that this group of patients was in the phase of intense block, in which it would have been necessary to administer 16 mg/kg of body weight of sugammadex in order to reverse the effect of rocuronium. The patients in this group received 4 mg/kg of body weight of sugammadex.

In the study presented in this paper, independently of the administered dose of sugammadex, the mean time of this drug's activity (T₀) was 1.11 minutes, which means that reversal of rocuronium's effect occurred almost immediately after administration of sugammadex. After administration of neostigmine, the reversal time for rocuronium was considerably longer, which has been confirmed in studies comparing the rate of both drugs.^{12,13} In the study from 2009, Mirakhur reported that the dose of 2 mg/kg of body weight of sugammadex reverses the block after rocuronium considerably faster than neostigmine in the dose of 50 µg/kg of body weight. In the first case TOFR = 0.9 was achieved after 1.9 minutes, in the second case it was after 17.6 minutes.¹⁴ Also other comparative studies showed that deep rocuronium-induced NMB was reversed much faster as a result of administering sugammadex (2.9 minutes) than neostigmine and glycopyrronium (50.4 minutes). No residual NMB was found subsequent to application of sugammadex.¹⁵ Administering neostigmine would have lengthened the reversal time of NMB, and apart from that in 10 patients it would not have been possible, as they were in the phase of deep relaxation in which it is inappropriate to use AchE inhibitors.

The key time to assess the rate of acting of sugammadex was T_5 – the time in which muscle strength returned to 90% of its initial value. T_5 was determined with the use of TOFR. TOFR = 0.9 reflects this correlation. The ESM patients reached T_5 in almost 24 minutes (23.8), while the MIV patients – in 28 minutes (28.3 minutes). This difference appeared to be statistically significant.

Another stage of the study which underwent evaluation was extubation time (T_e). In the ESM group it was by 3 minutes shorter than in the MIV group, yet this difference was not statistically significant. After 23–26 minutes patients were extubated and after anesthesiological evaluation of their general condition in the Aldrete's scale, they came back to their original ward. The effect of rocuronium in combination with sugammadex proved to be as short as the effect of mivacurium. Thus it can be concluded that rocuronium in connection with sugammadex became a short-acting relaxant.

Both relaxants were also compared for side effects. It is believed that unwanted effects subsequent to anesthetics occur in 1 of 10000 up to 1 of 20000 cases of general anesthesia. In 1 out of 6500 cases these are IgA-induced anaphylactic reactions, out of which 62% concern allergies to relaxants.¹⁶ As it was already mentioned, mivacurium is a drug which releases histamine.

In general, 6 unwanted effects were observed, they were most probably related to the use of relaxants. Five of them concerned mivacurium: redness of the face and neck, rash, bronchospasms, prolonged NMB. Two first complications did not have any effect on patients' condition and resolved without intervention after a few minutes subsequent to administering anesthesia (they concerned 3 patients). In 1 patient bronchospasm which surfaced as decreased arterial blood saturation and wheezes over lung fields identified through auscultation resolved after administering aminophylline and dexamethasone. The frequency of complications in the form of bronchospasm during anesthesia is assessed at the level of 0.17%–4.2%. In a comprehensive study in which 2022 publications from 1995–2005 were analyzed, it was concluded that vecuronium, rocuronium, cisatracurium and pancuronium are safe in asthmatic patients, while atracurium and mivacurium should be used in this group of patients very carefully as they may cause bronchospasms because of direct effect on muscarinic receptors.^{16,17} Other authors recommend not to use mivacurium in asthmatic patients and to consider application of alternative drugs. It is also not recommended to reverse NMB with neostigmine and other AChE inhibitors because of increased secretion and hypersensitivity of bronchia induced by these drugs.¹⁸

In the present study, among side effects after mivacurium, in 1 patient prolonged NMB occurred, which lasted 45 minutes, and then a spontaneous recovery of muscular strength occurred, which made extubation safe. It is commonly thought that rocuronium gives little vagolithic effects and in a wide range of doses it does not lead to a considerable release of histamine.¹⁶ Levy et al. assessed hemodynamic effects and release of histamine after admin-

istration of rocuronium dependent on the dose (0.6-0.9-1.2 $\mu\text{g}/\text{kg}$ of body weight, which corresponds to 2-3-4x ED95). They monitored the circulatory system and measured the level of histamine. They found minimal effect of the drug on hemodynamics and minimal release of histamine in such a wide range of doses.¹⁹ Obviously, this does not mean that rocuronium does not cause allergic response. As all steroidal relaxants, rocuronium has a quaternary ammonium ion considered to be a trigger of allergic response. In epidemiologic studies performed in France, the percentage of allergic reactions related to rocuronium proved higher than that in the case of mivacurium.¹⁷ In a Polish study on 3560 patients anesthetized with the TIVA method with the use of suxametonium, rocuronium, pancuronium and cisatracurium, the percentage of anaphylaxis after rocuronium constituted 7.02%. The authors of the study stated, however, that the presented results were only estimation, they were most probably exaggerated and should be considered carefully, as diagnosing allergy is not possible only on the basis of clinical findings.¹⁸ Sugammadex encapsulates rocuronium, it eliminates the ammonium ion. Is it then a drug which makes it possible to safely stop an allergic reaction? It is a really interesting research issue which has been recently analyzed. In the present study, when mivacurium and rocuronium were compared considering allergic response, no statistically significant differences were found, yet the study concerns a small group of patients. However, every unwanted reaction poses a serious problem for an individual patient, and its consequences can be dangerous. It is necessary to aim at using such anesthesiological techniques and selecting such drugs that minimize possible side effects. Patients with history of allergies constitute a growing group among patients who need anesthesia. Also, bronchial asthma is a problem of a growing percentage of population. In such cases, mivacurium should be excluded and rocuronium should be regarded as a drug which has fewer side effects. If studies finally confirm the possibility to stop a potential allergic reaction through administering sugammadex, the sugammadex-rocuronium complex shall prove to be a perfect solution in patients with positive history of allergy.²⁰

6. CONCLUSIONS

- (1) Intubation conditions evaluated with the Krieg scale are as good for mivacurium as for rocuronium.
- (2) The beginning of acting time determined by achieving deep blocking (TOF = 0) occurs sooner for rocuronium than for mivacurium. Surgical conditions to perform the operation assessed by the operator in its 10th minute according to the Krieg scale are better for rocuronium than for mivacurium.
- (3) After administering a single intubation dose of an intermediate-acting relaxant, that is rocuronium, and reversing its activity with sugammadex, muscular relaxation resolves faster than in the case of a single intubation dose of a short-acting relaxant, that is mivacurium.

- (4) The frequency of unwanted effects is similar for mivacurium and rocuronium.

The above conclusions allow one to state that in procedures whose duration is impossible to determine beforehand, such as intralaryngeal microsurgery, a rocuronium-sugammadex complex constitutes a good alternative for mivacurium, especially in patients with positive history of allergy.

Conflict of interest

None.

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None declared.

Ethics

The study was approved by the Bioethical Committee of the Warmia and Mazury Regional Medical Council in Olsztyn (the decision of 22 June 201, no 364/2010/BIOET).

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