ORIGINAL ARTICLE

Comparison of intubation condition and the quality of muscle relaxation between rocuronium and vecuronium using „timing principle“

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ABSTRACT

Aim To compare the quality of the conditions for endotracheal intubation and muscle relaxation between rocuronium bromide and vecuronium bromide using the ‘’timing principle’’ method for induction in anaesthesia. The “timing principle” includes the administration of muscle relaxants before the hypnotic agent during induction in anaesthesia.

Method Sixty patients who had undergone elective surgery were randomly allocated into two equal groups using muscle relaxants: rocuronium (group R) and vecuronium (group V). The intubation conditions were assessed using Cooper’s scoring system, based on jaw relaxation, vocal cords position and response to intubation. The quality of muscle relaxation was evaluated by recording the time of clinical weakness, a count of ‘’train of four’’ (TOF) twitches at intubation, the time of loss TOF response and duration of direct laryngoscopy.

Results The intubation conditions were excellent in 100% of patients in the group R versus excellent in 80% and good in 20% of patients in the group V ($p<0.05$). The time of clinical weakness was statistically significantly shorter in the group R than in the group V ($p<0.000$). The time of loss of TOF response was statistically significantly shorter in the group R ($p<0.000$). The absence of TOF twitches (the level of muscle relaxation of 100%) at intubation recorded in 25 (83.3%) patients in the group R versus five (16.7%) patients in the group V ($p<0.000$). Duration of direct laryngoscopy did not significantly differ between the groups.

Conclusion Rocuronium bromide provides better intubation conditions and greater quality of muscle relaxation than vecuronium bromide using ‘’timing principle’’ technique.

Key words: direct laryngoscopy, endotracheal intubation, neuromuscular monitoring, onset time, rapid sequence induction, vocal cords

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INTRODUCTION

The risk of vomiting and aspiration of gastric content during anaesthesia induction is one of the factors contributing to aesthetic morbidity and mortality. Endotracheal intubation is a mandatory procedure for securing airway in general anaesthesia practice (1). Rapid sequence intubation (RSI) technique minimizes the time between the loss of consciousness and tracheal intubation in order to protect the respiratory tract from gastric regurgitation and aspiration. The role of muscle relaxants is to achieve an appropriate level of muscle relaxation and facilitate endotracheal intubation (2). An ideal muscle relaxant should have a rapid onset of activity, brief duration of activity, provide excellent intubation conditions and be free from side effects. For more than 40 years, suxamethonium chloride was the gold standard relaxant for rapid sequence intubation because of its rapid onset (30-40 seconds), excellent intubation conditions and brief duration of activity (5-10 minutes) (3). Depolarising mechanism of action causes many side effects of suxamethonium: dysrhythmias, hyperkalemia, fasciculations and postoperative myalgia, increase of intraocular and intracranial pressure, triggering malignant hyperthermia and is contraindicated in burns, muscular dystrophy, spinal cord injuries, in patients with low cholinesterase activity or genetically aberrant enzyme (4). Various techniques of RSI have been used to avoid side effects of suxamethonium and accelerate the onset of nondepolarizing muscle relaxants activity: "timing principle", "priming principle" and "high-dose regimen" (5). In the "timing principle" technique a single bolus dose of nondepolarizing muscle relaxant is rapidly administered and anaesthesia is induced at the appearance of the first signs of clinical weakness. This technique shortens the time from the loss of consciousness until endotracheal intubation. The peak effect of the muscle relaxant and intravenous induction agent closely coincide (6). Rocuronium bromide is a newer aminoseroidal nondepolarizing musle relaxant with rapid onset and intermediate duration of activity (60 - 90 seconds) and may presents an alternative to suxamethonium for RSI in the situations when suxamethonium is contraindicated (7). Vecuronium bromide is a routinely used monoquaternary aminosteroid nondepolarizing muscle relaxant, with minimal hemodynamic side effects (8).

In our daily anaesthesia practice, suxamethonium is commonly used for RSI, but due to its numerous side effects, we decided to introduce the ''timing principle" for RSI. This method makes it possible to avoid suxamethonium in situations when it is contraindicated.

The aim of this study was to compare the quality of the conditions for endotracheal intubation and quality of the muscle relaxation between two muscle relaxants rocuronium and vecuronium using the method ''timing principle" for RSI. Additionally, the patient's personal satisfaction with anaesthesia induction among different muscle relaxants was compared.

METHODS

Patients and study design

This prospective randomized double-blinded clinical study was conducted at the Department of Anaesthesiology and Intensive Care Unit in Cantonal Hospital Zenica, Bosnia and Herzegovina over the period of six months, between January and July 2018. A total of 60 adult patients were recruited for the study. Inclusion criteria were: patients aged 18-60 years without predictive signs of difficult intubation, with the physical status grade I – III according to the American Society of Anesthesiologists (ASA) (9), all underwent endotracheal intubation and general anaesthesia for various elective surgical procedures. Exclusion criteria were: emergency surgery, patients with increased risk of aspiration or gastroesophageal regurgitation, neuromuscular disease, the use of drugs interfering with the neuromuscular transmission of impulses, contraindications and history of allergy to rocuronium and vecuronium.

The day before surgery preanesthetic examination of medical documentation and cardiopulmonary status of patients was conducted as well as a preoperative airways estimation for each patient. Airways assessment included: Mallampati score (10), chin-hyoid distance, flexio-extension of cranial spine mobility and the distance between incisors at the maximum open mouth. Patients with Mallampati grade III and IV, the chin-hyoid distance <3 cm, inability to touch the chest bone with their chin and the distance between incisors at the maximum open mouth <3 cm were considered at risk of difficult endotracheal intubation and were excluded from the study.

After providing an informed consent, the patients who fulfilled eligibility criteria were randomly allocated to two equal groups of 30 patients. Depending on the type of muscle relaxant used for anaesthesia induction, the groups were labelled as: group R (rocuronium bromide was used), group V (vecuronium was used). Randomization codes were computer generated using Microsoft Excel and held in sealed opaque envelopes. Before entering an operating room a nurse opened envelopes and handed a code to the anaesthesiologist. Patients, anaesthesiologist who performed anaesthesia induction and persons involved in data collection were blinded to the study protocol to ensure statistical validity and reliability.

The Ethics Committee of Cantonal Hospital Zenica approved the study protocol.

Methods

Anaesthesia protocol. Patients were maintained nil by mouth eight hours prior to the surgery. In the preanesthesia room, an intravenous cannula of 18G was placed into the hands of all patients. After the start of Ringer-lactate infusion fluids in a dose of 5 mL/kg, patients were premedicated with midazolam 0.03 mg/kg and fentanyl 1 μg/kg. In the operating room, standard clinical monitoring was performed: pulse oximetry, noninvasive arterial blood pressure, the electrocardiogram and capnography. Neuromuscular block monitoring was placed on the hand opposite the site of the intravenous cannula. Three minutes before induction, all patients were preoxygenated with 100% oxygen by facial mask.

In the group R, rocuronium bromide 0.6 mg/kg was given intravenously, within 5 seconds. In the group V, vecuronium bromide 0.1 mg/kg was given intravenously. The patients were asked to keep their eyes open as long as possible. The anaesthesiologist carefully observed the appearance of ptosis of eyes. At that moment anaesthesia induction by propofol 2 mg/kg intravenously was started. Simultaneous stimulation of ulnar nerve at wrist was applied using four supra maximal square wave stimuli – ''train of four" (TOF) of 2 Hz and was repeated every 12 seconds. Sixty seconds after the application of propofol, endotracheal intubation was performed in both groups. Only one attempt of endotracheal intubation was made for each patients. If the patients required two intubation attempts, they would be excluded from the study. Balanced general endotracheal anaesthesia was maintained by sevoflurane minimum alveolar concentration 0.5-1‰, N_2O 50% in oxygen**,** at a total flow of 2 L/min. The patients were ventilated with a tidal volume 6 mL/kg and respiratory rate 10-12/min. End tidal carbon dioxide was maintained at 30-35 mmHg. At the end of surgery, neuromuscular block was reversed with neostigmin 0.05 mg/kg and atropin 0.02 mg/kg and the patients were extubated fully awake.

Evaluation of the quality of intubating conditions. The intubation conditions were evaluated as per the scoring system described by Cooper et al. (11). The system includes three parameters: jaw relaxation, vocal cords position and response to intubation. Jaw relaxation was graded as follow: 0-impossible, 1-opens, 2-moderate and 3-easy. Vocal cords position was ranked: 0- closed, 1-closing, 2-moving and 3-open. Response to intubation was scored: 0-severe coughing, 1-mild coughing, 2-slight diaphragmatic movement and 3-no movement. Intubating conditions were scored ''excellent" if the sum was 8-9, ''good" if the sum was 6-7, ''fair" for the sum 3-5 and ''poor" for the sum 0-2.

Evaluation of the quality of muscle relaxation. The parameters of the quality of muscle relaxation were: the time of clinical weakness, a count of TOF twitches at intubation, the time of loss of TOF response and duration of direct laryngoscopy. The time of clinical weakness was defined as the time from application of muscle relaxant to the appearance of ptosis of eyes. A count of TOF twitches at the adductor pollicis muscle at intubation was the marker of the degree of muscle relaxation. The TOF stimulation causes the twitches of adductor pollicis muscle. Four twitches were considered as a complete response of muscle to TOF stimulation. Applying muscle relaxants caused sequential loss of TOF twitches. The fourth response disappeared the earliest, then the third, the second, and finally the first twitch, corresponding to the development of 75%, 80%, 90% and 100% of muscle relaxation. Acceptable degree of muscle relaxation for endotracheal intubation was the absence of the twitches on TOF stimulation.

The time of loss of TOF response was the marker of the complete muscle relaxation and was defined as the time from application of muscle relaxant to loss of all four twitches from TOF

stimulation. Duration of direct laryngoscopy was defined as a time from the placement of a direct laryngoscope blade in the mouth to the beginning of endotracheal tube cuff inflation. **Patient's subjective satisfaction with anaesthesia induction.** Six to 24 h after surgery, the patients were interviewed about the personal impression of anaesthesia induction. The questionnaire included the following questions: Did you feel shortness of breath, difficulty breathing, or any other change in breathing immediately before going to sleep for surgery? Did you have any discomfort or anxiety immediately before going to sleep for surgery? Did you feel pain of the injection during anaesthesia induction? Do you have any muscle pain now? If you had to sleep again for surgery, would you choose the same kind of anaesthesia? (12). The patients answered the questions with ''YES'' and ''NO''.

Evaluation of pain intensity during administration of rocuronium. Six to 24 h after surgery, patient's pain intensity during administration of rocuronium was evaluated by Visual Analogue Scale (VAS) (13). On one side the scale is horizontal, 10 cm long and non- graduated, with anchors at both ends. Common anchors are 0 cm "no pain" and 10 cm "the worst imaginable pain". The patient was asked to draw a vertical line through the horizontal line to indicate their pain intensity during application of rocuronium injection. On the other side of VAS scale, the staff who collected the data read the numerical value of patient's pain intensity. The cut points on the pain VAS had been recommended: no pain (0–4 mm), mild pain (5–44 mm), moderate pain (45–74 mm), and severe pain (75–100 mm). VAS ≤ 3 was accepted as pain without the need for analgesic drugs.

Statistical analysis

Sample size was estimated using sample size calculator software with 95% confidence interval and power of 80%. Statistical significance was considered as $p<0.05$. Categorical variables were analysed by Pearson's $\chi 2$ test and presented as frequency and relative number of cases (percentage). The parametric variables were expressed as means and standard deviation and analysed by Student's t test, one way analysis of variance (ANOVA) and Pearson's correlation as appropriate.

RESULTS

Data were obtained from 60 adult patients undergoing various elective surgical procedures. All patients were intubated at first attempt, completed the study and were analysed (Figure 1). The groups

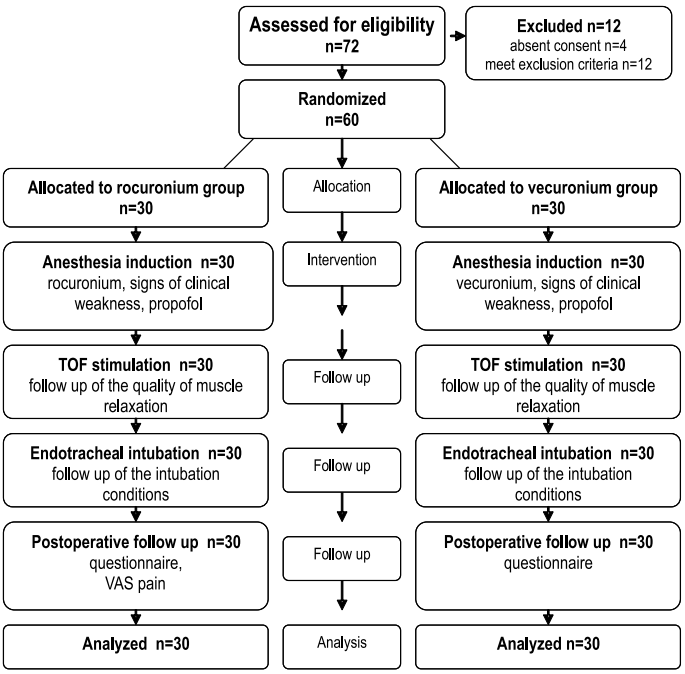

Figure 1. Flow chart (CONSORT diagram) of the study protocol
TOF, Train of four; VAS, Visual Analogue Scale;

were homogeneous and comparable. Demographic data, age, gender, body weight, body height, ASA physical status grade, Mallampati score and type of surgery did not differ between two groups (Table 1).

Table 1. Demographic characteristics of patients

Parameter	Group R	Group V	p
Age (years) mean (±SD)	50.8 (±9.7)	47.4± (11.9)	0.471
Male/Female No (%)	13/17 (43/57)	14/16 (46/54)	0.733
Body weight (kg) mean (±SD)	80.4 (±10.7)	85.6 (±11.8)	0.177
Body height (cm) mean (±SD)	169.8 (±7.7)	173.1 (±7.4)	0.213
ASA status grade I/II/III No (%)	15/15/0 (50/50/0)	12/18/0 (40/60/0)	0.604
Mallampaty score I/II No (%)	23/7 (77/23)	24/6 (80/20)	0.830
Type of surgery No (%)			0.631
Abdominal surgery	15 (60)	13 (43)	
Urology	13 (40)	2 (7)	
Gynaecology	0	11 (37)	
Otorhinolaryngology	1 (0)	0	
Plastic surgery	1 (0)	4 (13)	

Group R, rocuronium bromide group; Group V, vecuronium bromide group; SD, standard deviation; ASA, American Society of Anesthesiologist

Comparison of the parameters of the Cooper's scoring system showed that jaw relaxation and position of vocal cords were not statistically significantly different between group R and group V (p=1.000 and p=1.000, respectively). In response to intubation 30 (100%) patients had no movement in the group R, while 6 (20%) patients had mild coughing, 4 (13.3%) patients had slight diaphragmatic movement and 20 (64.7%) had no movement (p<0.015). Overall Cooper score of intubation conditions was statistically significantly better in the group R (Table 2).

Table 2. Comparison of the Cooper score system

Parameters of intubation conditions	Group	No (%) of patients according to the Cooper score				p
		0	1	2	3	
Jaw relaxation		**Impossible**	**Opens**	**Moderate**	**Easy**	**1.000**
	Group R	0 (0)	0 (0)	0 (0)	30 (100)	
	Group V	0 (0)	0 (0)	0 (0)	30 (100)	
Vocal cords		**Closed**	**Closing**	**Moving**	**Open**	**1.000**
	Group R	0 (0)	0 (0)	0 (0)	30 (100)	
	Group V	0 (0)	0 (0)	0 (0)	30 (100)	
Response to intubation		**Severe coughing**	**Mild coughing**	**Slight diaphragm movement**	**No of movement**	**0.015**
	Group R	0 (0)	0 (0)	0 (0)	30 (100)	
	Group V	0 (0)	6 (20)	4 (13.3)	20 (64.7)	
Overall Cooper score		**Poor (0-2)**	**Fair (3-5)**	**Good (6-7)**	**Excellent (8-9)**	**0.036**
	Group R	0 (0)	0 (0)	0 (0)	30 (100)	
	Group V	0 (0)	0 (0)	6 (20)	24 (80)	

Group R, rocuronium bromide group; Group V, vecuronium bromide group

The time of clinical weakness was statistically significantly shorter in the group R than in the group V (p<0.000) as well as the time of loss of TOF response (p<0.000). Duration of direct laryngoscopy did not significantly differ between the groups (Table 3).

Table 3. Comparison of the quality of muscle relaxation

Parameter	Group R	Group V	p
Time of clinical weakness (seconds) mean (±SD)	24.4 (±7.5)	37.4±7.5	0.000
Time of loss TOF response (seconds) mean (±SD)	90.9 (±21.0)	171.0±47.5	0.000
Duration of direct laryngoscopy (seconds) mean (±SD)	11.07 (±1.5)	11.67±2.5	0.867

Group R, rocuronium bromide group; Group V, vecuronium bromide group; SD, standard deviation; TOF, train of four

The absence of TOF twitches (the degree of muscle relaxation of 100%) at intubation was recorded in 25 (83.3%) patients in the group R versus five (16.7%) patients in the group V (p<0.000) (Table 4). Four TOF twitches (the level of muscle relaxation <75%) at intubation were recorded in one (3.3%) patient in the group R versus 18 (60%) patients in the group V (p<0.000).

Table 4. Comparison of the count of Train of four (TOF) twitches at intubation

Count of TOF twitches at intubation	% of muscle relaxation	No (%) of patients		p
		Group R	Group V	
0	100%	25 (83.3)	5 (16.7)	0.000
1	90%	1 (3.3)	1 (3.3)	1.000
2	80%	3 (10)	0 (0)	0.383
3	75%	0 (0)	6 (20)	0.001
4	<75%	1 (3.3)	18 (60)	0.000

Group R, rocuronium bromide group; Group V, vecuronium bromide group;

In both groups none of the patients felt any shortness of breath or difficulty breathing (p=1.000), and none of the patients felt any discomfort or anxiety immediately before going to sleep for surgery (p=1.000). There were no patients who had muscle pain at the time of interview in the group R and group V. All patients would choose the same kind of anaesthesia if they had to sleep again for an operation (p=1.000).

VAS pain analysis showed that 24 (80%) patients had no pain during administration of rocuronium. Four (13.3%) patients had mild pain and two (6.7%) patients had moderate pain. A total of six (20%) patients expressed pain during administration of rocuronium. There were no patients with VAS pain score ≥3 and the need of analgesic drugs.

DISCUSSION

The presented study compared the quality of the conditions for endotracheal intubation and muscle relaxation between rocuronium bromide and vecuronium bromide using ‘’timing principle“ technique for RSI. The intubation conditions produced by rocuronium bromide were excellent in 100% of patients, but produced by vecuronium bromide were excellent in 80% and good in 20% of patients. Rocuronium bromide achieved statistically significantly faster appearance of clinical weakness and complete muscle relaxation than vecuronium bromide. Rocuronium bromide reached the level of muscle relaxation of 100% at intubation in 83% of patients.

The RSI is based on rapid sedation, complete muscle relaxation and procurement of airway up to 60 seconds. Only suxamethonium provided adequate paralysis in less than one minute (14). Suxamethonium has occasional but unpredictable risks and clinicians prefer to use nondepolarizing muscle relaxants rocuronium and vecuronium in selected patients. Neither of these agents do not have an onset of activity fast enough as needed for RSI. The specific point of the “timing principle” is administration of muscle relaxant in awake patients, before an induction agent for the purpose of faster onset of muscle relaxation with nondepolarizing relaxants (15). Dosage of muscle relaxants is based on the value of 95 effective dose (ED) which is needed to produce 95% of neuromuscular blockade. The usual intubation dose is multiplied by the ED95 dose (16). In our study, rocuronium bromide of 0.6 mg/kg (2 x ED95) was used and compared with vecuronium bromide of 0.1 mg/kg (2 x ED95).

Intubation conditions are determined by clinical criteria, such as jaw relaxation, vocal cord movement and diaphragmatic relaxation. In this study, rocuronium 2 x ED95 produced excellent intubation conditions at 60 seconds, and vecuronium 2 x ED95 produced excellent and good intubation conditions. The reason for less excellent intubation conditions in the group V (vecuronium) were diaphragmatic movements and mild cough as a response to intubation possibly due to longer onset of vecuronium activity. This result is corroborated with Parasa et al. study (17). In the study of Shareef et al. poor intubation conditions were found in 12% patients at 60 seconds with rocuronium and in 40% patients with vecuronium using classical technique of RSI, not “timing principle” (18).

In this study, rocuronium significantly accelerated onset of the signs of clinical weakness as compared to vecuronium. Those results were consistent with Chatrath et al. study (19). Shajahan et al. found earlier appearance of ptosis than in our study, but they applied rocuronium 3 x ED95 (20). Rocuronium reached a loss of TOF response or complete muscle relaxation much earlier than vecuronium in the presented study, which is comparable with Mohanty et al. results (21). Complete muscle relaxation was even faster if rocuronium 3 x ED was used with ‘’timing principle“ (22). Complete muscle relaxation with rocuronium of 0.6 mg/kg was 19 seconds slower than in our study when ‘’timing principle“ was not applied (23).

Acceptable degree of muscle relaxation at intubation or absence of TOF twitches was reached in 83.3% patients with rocuronium and in 16.7% patients with vecuronium. According to neuromuscular monitoring 60% patients in the group V showed inadequate muscle relaxation at intubation but they had excellent or good intubation conditions according to clinical criteria. The reason for such a discrepancy between neuromuscular monitoring and clinical criteria is a faster onset of muscle relaxation in centrally located muscles diaphragm and laryngeal muscles than in peripheral adductor pollicis muscle (24)

The „timing principle“ technique has a potential risk of patient’s anxiety during anaesthesia induction since the clinical weakness precedes loss of consciousness. In order to avoid patient’s awareness and discomfort we premedicated patients with midazolam that caused anterograde amnesia. In the questionnaire conducted after surgery all patients expressed satisfaction with anaesthesia induction. In the study of Kamalakannan and Sunder, authors did not use midazolam. The patients were premedicated with fentanyl and in a postoperative questionnaire 6% patients complained about shortness of breath before anaesthesia induction (25).

Pain on rocuronium bromide injection has been reported in 50-80% patients (26). In the ‘’timing principle“ technique, precautions should be taken for the pain sensation on rocuronium injection in awake patients. The use of sodium bicarbonate,

local anaesthetics, opioids and antihistamines proved to be effective (27). In our study, 20% of patients expressed pain during administration of rocuronium. Lower incidence of pain in comparison to the literature was probably caused by the combination of hypnotic and opioid drugs used in premedication. Mild and moderate pain intensity was recorded that did not require analgesic therapy.

This study has some limitations. The hemodynamic stress response during endotracheal intubation was not assessed. The analysis should include serum stress indicators, such as glycaemia and cortisol. This study was conducted in selected patients prepared for elective surgery. For patients with critical illness, it may be necessary to adjust dosage regimens.

In conclusion, the "timing principle" technique with 0.6 mg/kg rocuronium bromide is safe, reliable and comfortable method for RSI. Rocuronium bromide provides excellent intubation conditions and greater quality of muscle relaxation 60 seconds after administration compared to vecuronium bromide. The "timing principle" technique with rocuronium bromide could be recommended for RSI when suxamethonium is contraindicated.

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Competing interest: none to declare

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