Comparison of Neuromuscular Blockade with Two Different Agents After A Priming Dose of Rocuronium: A Randomized Clinical Trial

Rokuronyumla Başlangıç Dozu Sonrasında İki Farklı Ajanla Nöromusküler Blokajın Kıyaslanması: Randomize Klinik Çalışma

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ABSTRACT Objective: The purpose of this study was to assess the pharmacological effects of a priming dose of rocuronium in combination with the non-depolarizing blockers rocuronium or vecuronium during the perioperative period. **Material and Methods:** Sixty patients with American Society of Anesthesiologists (ASA) risk status I or II scheduled to receive anesthesia for elective surgery were included in the study. Patients were randomly divided into four groups. Patients in Group I (n=15) received a priming dose of normal saline and rocuronium bromide 0.6 mg/kg following induction of anesthesia; patients in Group II (n=15) received a priming dose of normal saline and vecuronium bromide 0.1 mg/kg following induction; patients in Group III (n=15) received a priming dose of rocuronium bromide 0.1 mg/kg followed by rocuronium bromide 0.6 mg/kg after induction; and Group IV (n=15) patients received a priming dose of rocuronium bromide 0.1 mg/kg followed by vecuronium bromide 0,1 mg/kg. T95 (time to onset of action), T25 (clinical duration of action), T75 (total duration of action) and recovery index (RI) were measured and recorded. Patients were monitored for possible side effects. **Results:** In Group III, in which patients were primed with rocuronium and maintained with rocuronium, the time to onset of action was significantly shorter than for patients in Group I. Similarly, this parameter was significantly shorter in Group IV patients than in Group II patients. T25 and T75 was significantly longer in Group II and Group IV than in the other groups. There was no significant difference in RI values between the groups. **Conclusion:** Using rocuronium as a priming agent accelerates the neuromuscular blocking effects of both rocuronium and vecuronium and provides ideal intubation conditions when safe and quick intubation is required.

Key Words: Neuromuscular blockade; rocuronium; vecuronium bromide

ÖZET Amaç: Bu çalışmanın amacı, nondepolarizan nöromusküler bloker olarak rokuronyum ve vekuronyum kullanımı sırasında rokuronyumla başlangıç dozu uygulamasının perioperatif dönemdeki farmakolojik etkilerini araştırmaktır. **Gereç ve Yöntemler:** Elektif cerrahi için anestezi alması planlanmış, American Society of Anesthesiologists (ASA) risk statüsüne göre grup I veya II'ye giren altmış hasta çalışmaya dahil edildi. Hastalar randomize olarak dört gruba ayrıldı. Grup I'deki hastalara (n= 15) serum fizyolojik ile başlangıç dozu, anestezi indüksiyonunu takiben rokuronyum bromid 0.6 mg/kg uygulandı; Grup II'deki hastalara (n= 15) serum fizyolojik ile başlangıç dozu, anestezi indüksiyonunu takiben vekuronyum bromid 0,1 mg/kg uygulandı; Grup III'teki hastalar (n= 15) rokuronyum bromid 0,1 mg/kg başlangıç dozunu takiben indüksiyonun ardından rokuronyum bromid 0,6 mg/kg dozunu aldılar ve Grup IV'teki hastalara (n= 15) rokuronyum bromid 0,1 mg/kg başlangıç dozunu takiben vekuronyum bromid 0,1 mg/kg verildi. T95 (etki başlama süresi), T25 (klinik etki süresi), T75 (total etki süresi) ve derlenme endeksi (DE) ölçüldü ve kaydedildi. Hastalar olası yan etkiler açısından izlendi. **Bulgular:** Başlangıç dozu olarak rokuronyum uygulanan hastaların oluşturduğu Grup III'te etkinin başlama süresi, Grup I'e göre anlamlı ölçüde daha kısaydı (Grup III için T95134 s Group I için T95160 s) (p= 0,006). Benzer şekilde bu parametre, Grup IV'teki hastalarda Grup II'deki hastalara göre anlamlı düzeyde daha kısaydı (Group IV için T95 152 s Group I için T95187 s) (p< 0,001). Grup II ve Grup IV'teki hastaların T25 ve T75 değerleri diğer gruplara göre daha uzundu. Gruplar arasında Dİ değerleri açısından anlamlı farklılık saptanmadı. **Sonuç:** Rokuronyumu başlangıç ajanı olarak kullanmak, hem rokuronyumun hem de vekuronyumun nöromusküler blokaj etkilerini hızlandırır ve güvenli ve hızlı entübasyon gerektiğinde ideal entübasyon ortamı sunar.

Anahtar Kelimeler: Nöromusküler blokaj; rokuronyum; vekuronyum bromür

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Endotracheal intubation and the use of neuromuscular blocking agents (NMBA) play an important role in general anesthesia. The period between the administration of neuromuscular blocking drugs and establishing adequate intubation conditions is considered the most critical period of anesthesia for avoiding hypoxia and pulmonary aspiration episodes.[1] With reasonable doses of non-depolarizing blocking drugs, reliable conditions for intubation cannot be achieved in less than two to three minutes.[2] The onset of the effect of depolarizing blocking agent succinylcholine is observed in 10-30 seconds but it has serious side effects, including muscle pain due to fasciculations, bradycardia, hyperkalemia, ventricular arrhythmias and malign hyperthermia.[3] Routine use of succinylcholine remains controversial due to reported cases of serious arrhythmia and cardiac arrest.[3] Recent studies using non-depolarizing blocking agents for endotracheal intubation have reported different methods to shorten this period.[4,5]

The "priming principle" is a recent commonly used approach to accelerate the effect of the basic drug by reducing the sensitivity of acetylcholine receptors by the administration of non-depolarizing blocking agents in sub-paralytic doses. This technique consists of the administration of a small dose of NMBA prior to the remaining dose. Thus, a rapid onset effect of NMBA is achieved.[6,7] This small initial dose was termed as the "priming dose" by Foldes.[8] If the initially administered non-depolarizing agent for priming is different from the basic non-depolarizing agent, dose requirement and prolongation of action of the basic drug may change due to interactions between the two drugs.[9]

The aim of this study was to examine the perioperative pharmacological effect of the priming dose rocuronium during the use of rocuronium or vecuronium as the main essential NMBA.

MATERIAL AND METHODS

A prospective study was conducted at the Göztepe Training Hospital on 60 patients between 26 and 68 years of age who were scheduled for repair of disc herniation. Informed consent was obtained from each participant and the study protocols were reviewed and approved by the Göztepe Training Hospital Local Ethics Committee. The study was carried out according to institutional guidelines. All patients were classified as American Society of Anesthesiologists (ASA) I or II and Mallampati I or II. Only patients with a body mass index of 20-30 were included in the study. Patients with cardiovascular, neuromuscular, renal and hepatic illnesses, patients who had taken drugs capable of influencing neuromuscular functions (e.g., magnesium sulphate, anticonvulsants and polypeptide antibiotics), patients who had radiotherapy or chemotherapy, and patients with malnutrition or alcohol abuse were excluded from the study. Patients with an error in neuromuscular monitor calibration and those with a peripheral temperature of < 32°C were also excluded.

Sixty patients were randomized into four groups in this prospective, randomized study design. The following non-invasive hemodynamic parameters were recorded; heart rate (HR), peripheral oxygen saturation (SpO^2), mean arterial pressure (MAP), respiratory rate, end-tidal CO^2 ($ETCO^2$) and inspiratory sevoflurane concentrations (Datex-Ohmeda S/5, Finland). Musculus adductor pollicis muscle and ulnar nerve were used for neuromuscular monitoring. Single twitch T1 and train-of-four (TOF) stimuli were chosen for neuromuscular stimulation (TOF watch-Organon teknika, Netherlands). Patients were premedicated with intravenous midazolam 0.03 mg/kg and fentanyl 1 mcg/kg. TOF-Guard calibration was performed after pre-medication. The response height of the adductor pollicis muscle to single control stimulation and TOF were 100% calibrated, and stimulations were discontinued when muscle relaxants were administered.

In this prospective randomized study, patients were allocated to each group using a computer-generated table of pseudo-random numbers. The four groups were as follows; Group I, priming with normal saline, 0.6 mg/kg rocuronium bromide administered following anesthesia induction; Group II, priming with normal saline, 0.1 mg/kg vecuronium bromide administered following anesthesia induction; Group III, priming with 0.1 mg/kg

rocuronium bromide, 0.6 mg/kg rocuronium bromide administered following anesthesia induction and Group IV, priming with 0.1 mg/kg rocuronium bromide, 0.1 mg/kg vecuronium bromide administered following anesthesia induction.

Priming dose was administered three minutes before induction. In all patients, anesthesia was induced with sodium thiopenthal 5 mg/kg. T_{95} (the time in seconds from drug administration to the achievement of 95% block) was detected by neuromuscular monitoring. When response to stimulations decreased to <5%, the patients were intubated by the same anesthetist. The quality of endotracheal intubation was evaluated by the Clarke and Mirakhur Scale (CMS) (Table 1).

Anesthesia was maintained with Sevoflurane 1% and 50% N_20/O^2. Mechanical ventilation was initiated to keep $ETC0^2$ constant at 30-35 mmHg and peripheral skin temperature was kept above 32°C. The onset of action of muscle relaxants (times from the injection to 95% depression according to baseline values in single stimulation), clinical duration of action (time to 25% recovery to baseline values in a single stimulation), and recovery time (time for 25 to 75% recovery of T1 in single stimulation) were monitored by responses to four serial stimulations at 15-second intervals and were recorded. Hemodynamic parameters were recorded at five-minute intervals before induction, before intubation, after intubation and during surgery. After administration of the muscle relaxant, patients were monitored for possible side effects such as arrhythmia, bronchospasm, pruritus, edema, anaphylactic or anaphylactoid reaction.

STATISTICAL ANALYSIS

Data were analyzed using SPSS for Windows 10.0. Chi square test was used for comparisons of categorical parameters. Continuous variables between the four groups were compared using the Kruskal-Wallis test. If the difference was significant, Mann-Whitney U test was used to compare data pairs. $p< 0.05$ was considered statistically significant.

RESULTS

Groups did not differ with regard to demographic data (Table 2). T_{95} was significantly shorter in Group III compared to Group I (134 sec vs 160 sec, respectively) ($p= 0.006$) and in Group IV compared to Group II (152 sec vs 187 sec, respectively) ($p< 0.001$). In Group III, T_{95} was significantly shorter than that of other groups and similarly, it was significantly shorter in Group III and Group IV than

TABLE 1: Clarke and Mirakhur evaluation scale.

Score	Chin relaxation (Laryngoscopy)	Vocal Cords	Reaction to Intubation
0	Impossible	Closed	Forceful coughing or strain
1	Difficult	Semi-closed	Moderate strain
2	Moderate	Active	Mild diaphragmatic movement
3	Easy	Open	No reaction

Scoring: 8-9 excellent; 6-7 good; 3-5 average; 0-2 poor.

TABLE 2: Demographic properties of the patients.

		Group I	Group II	Group III	Group IV	P
Age (year)+		42 (30-59)	47 (27-68)	46 (30-63)	44 (26-63)	0.663
Weight (kg)+		68 (57-94)	77 (48-100)	72 (52-90)	68 (55-90)	0.266
Height (cm)+		168 (155-188)	166 (150-180)	165 (152-180)	160 (155-176)	0.277
BMI (kg/m^2)+		23.63 (21.19-28.58)	27.18 (21.16-29.75)	27.16 (22.51-29.05)	24.21 (20.02-29.98)	0.142
Gender	Male*	8 (53.3%)	7 (46.7%)	7 (46.7%)	10 (66.7%)	
	Female*	7 (46.7%)	8 (53.3%)	8 (53.3%)	5 (33.3%)	0.658

For each group n=15; + presented as median (min-max); * number of patients (%), BMI: Body mass index.

in Group II ($p< 0.001$) (Table 3, Figure 1A). T_{25} and T_{75} were significantly longer in Group II and Group IV than in the other groups (Table 3, Figure 1B). There was no significant difference between groups in terms of RI (Table 3). Evaluation of intubation conditions with CMS showed excellent results in all cases. However, CMS values in Group IV were significantly higher than in Group I and in Group III (Table 3, Figure 1C). There was no significant difference between groups with regard to MAP, HR, SpO_2 and $ETCO_2$ values ($p> 0.05$). There was no significant difference between groups in terms of side effects ($p> 0.05$). None of the patients showed signs or symptoms of histamine release, including arrhythmia, bronchospasm, pruritus and edema, or anaphylactic or anaphylactoid reaction. Only two patients during rocuronium injection and one patient during calibration of the neuromuscular monitoring equipment reported pain.

DISCUSSION

Due to its fast onset of action and safety profile, rocuronium is one of the most widely used relaxants in many countries. [10] Several methods have been attempted to shorten the onset of action of non-depolarizing agents without changing standard intubation doses. "Priming" is one of these methods and an ideal priming dose is expected to accelerate the onset of action without any side effects. A priming dose consisting of 10% of the intubation dose with a three to four minute priming interval has been considered reliable and effective.[5,11] Recently, priming doses of agents other than the non-depolarizing neuromuscular blocking agents have been used to benefit from their synergistic effects.[12,13] Rashkovsky et al. suggested in their study on pancuronium and vecuronium that the formerly administered drug appeared to have a significant impact on both dose requirements and duration of action of the subsequent neuromuscular blocker.[9]

In this study, T_{95} was significantly shorter in the group receiving a priming dose of rocuronium (Group III) than in the single dose rocuronium group (Group I), and in the vecuronium group primed with rocuronium (Group IV) compared to the single dose vecuronium group (Group II). These findings are similar to the results of Naguib et al. and Bock et al.[14,15] In the study by Naguib et al., 70 patients were randomly assigned into seven groups.[14] Group I received single dose mivacurium 0.15 mg/kg; Group II received a priming dose of mivacurium 0.015 mg/kg and mivacurium 0.135 mg/kg three minutes later; Group III received a single dose rocuronium 0.6 mg/kg; Group IV received a priming dose of rocuronium 0.06 mg/kg and rocuronium 0.54 mg/kg three minutes later, Group V received a priming dose of mivacurium 0.015 mg/kg followed by rocuronium 0.54 mg/kg; Group VI received a priming dose of rocuronium 0.06 mg/kg followed by mivacurium 0.135 mg/kg; and Group VII received

TABLE 3: Comparison of intubation conditions, T_{95}, T_{25}, T_{75} and RI values between groups.

	Group I	Group II	Group III	Group IV	P
CMS	8 (6-9)[a]	9 (6-9)	8 (8-9)[j]	9 (8-9)	0.014
T95 (sec)	160 (136-190)[b,e]	187 (128-270)[f,i]	134 (89-180)[k]	152 (134-191)	<0.001
T25 (min)	31 (16-57)[c]	38 (32-50)[g]	32 (15-45)[l]	44 (22-50)	0.004
T75 (min)	38 (21-87)[d]	44 (37-60)[h]	40 (25-50)[k]	57 (26-64)	0.019
RI (min)	7 (4-36)	6 (5-10)	8 (5-15)	9 (5-14)	0.053

[a]: for Group I vs Group IV p= 0.010, [b]: for Group I vs Group II p< 0.001, [c]: for Group I vs Group II p= 0.003, [d]: for Group I vs Group II p= 0.041, [e]: for Group I vs Group III p= 0.006,
[f]: for Group II vs Group III p< 0.001, [g]: for Group II vs Group III p= 0.002, [h]: for Group II vs Group III p= 0.033, [i]: for Group II vs Group IV p< 0.001,
[j]: for Group III vs Group IV p= 0.029, [k]: for Group III vs Group IV p= 0.008, [l]: for Group III vs Group IV p= 0.019.

CMS: Clarke and Mirakhur Scale

T95: The onset of action of muscle relaxants (times from the injection to 95% depression according to baseline values in single stimulation).

T25: Clinical duration of action (time to 25% recovery to baseline values in a single stimulation).

T75: Time to 75% recovery to baseline values in a single stimulation.

RI: Recovery index (time for 25 to 75% recovery of T1 in single stimulation).

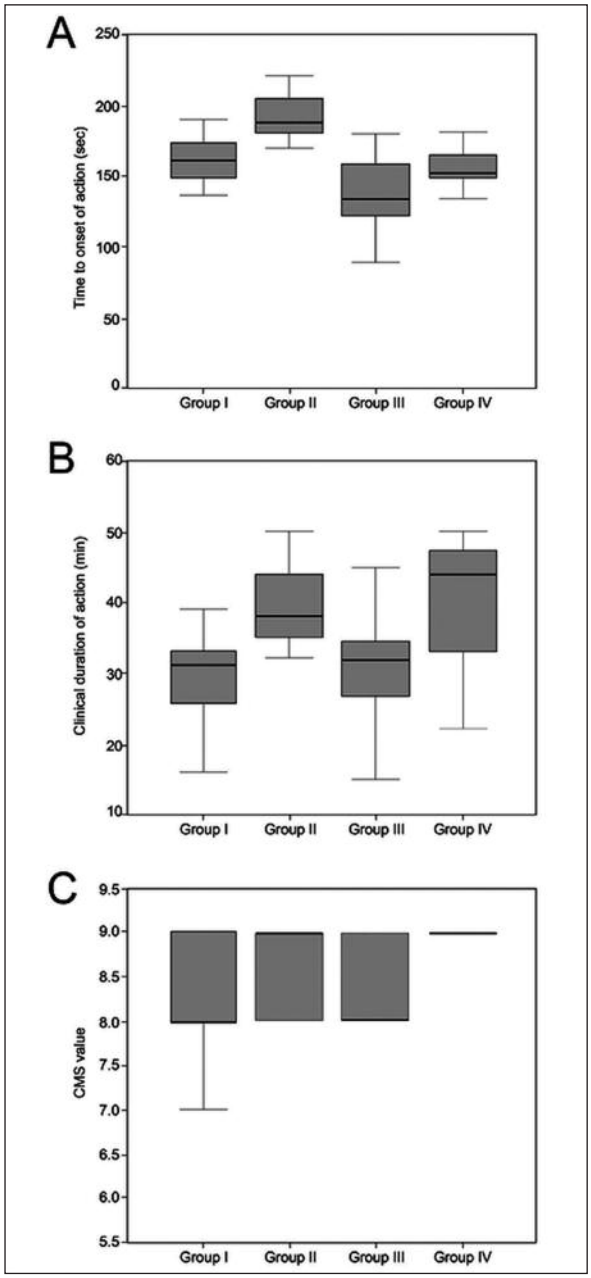

FIGURE 1: Intergroup comparisons of onset of action **(A)**, clinical duration of action **(B)**, and CMS values **(C)**. CMS, Clarke and Mirakhur Scale.

succinylcholine 1.0 mg/kg. In that study, time to onset of action in Groups IV (73 ± 16 s) and VI (58 ± 11 s), where priming was performed with rocuronium and followed by rocuronium or mivacurium, was similar to the succinylcholine group and was significantly shorter than in the other groups ($p< 0.01$). There was no difference between the groups in terms of intubation quality.[14]

Bock et al. examined the effects of different priming approaches before rocuronium administration in 84 patients.[15] Patients were divided into four groups; Group I received rocuronium 0.45 mg/kg one minute after placebo serum saline injection; Group II received a priming dose of rocuronium 0.045 mg/kg followed by rocuronium 0.45 mg/kg one minute later; Group III received placebo saline injection one minute before rocuronium 0.6 mg/kg; and Group IV received a priming dose of rocuronium 0.06 mg/kg and rocuronium 0.54 mg/kg one minute later. Times to the onset of action were significantly shorter in Group II (92.5 ± 24 sec.) than in Group I (122.5 ± 54 s) ($p< 0.05$), and in Group IV (55 ± 17 s) than in Group III (85 ± 25 s) ($p< 0.05$). The investigators concluded that priming with rocuronium significantly shortened T_{95} onset of action.[15]

On the other hand, Ramsey et al. reported different results.[16] They assigned 19 patients into two groups. They administered a priming dose of atracurium 50 μg/kg followed by atracurium 350 μg/kg four to five minutes later to Group I and a 400 μg/kg single dose of atracurium without priming to Group II, and found no significant difference between the groups in terms of time to onset of action. Similarly, Foldes et al. administered a priming dose of rocuronium 0.1 mg/kg and rocuronium 0.5 mg/kg as an intubation dose with a four-minute priming interval and showed that there was no change in time to onset of action.[17] When the priming interval exceeded the optimal time interval of priming principle, onset of action of the intubation dose was significantly delayed.[16] As a result, the four-minute priming interval used by Foldes et al. does not seem optimal for rocuronium since it may cause a delay in action. This effect may be related to the rapid onset of action of rocuronium.

Ortiz-Gomez et al. administered a priming dose of rocuronium, atracurium, cis-atracurium, vecuronium and mivacurium equivalent to 10% of the intubation dose or saline and subsequently rocuronium equivalent to 90% of intubation dose four minutes later.[18] Intubation quality was significantly higher in the priming group than in the control group and the priming dose equivalent to

10% of the intubation dose was considered appropriate and reliable.[18] In a study of Leykin et al., 60 patients were assigned into two groups.[19] Group I received a priming dose of 0.04 mg/kg followed by 0.4 mg/kg rocuronium three minutes later. In the second group, the same procedure was performed with saline solution instead of rocuronium for priming. Intubation quality for the groups was recorded. The quality of intubation was significant higher in the priming group ($p< 0.05$).[19]

In this study, patients were intubated by the same anesthetist and were evaluated with the CMS. An increased number of patients in the priming groups (Groups III and IV) presented with excellent intubation conditions. The average CMS value for Group I was lower than that of Group IV. This non-significant difference may be related to the physiologic and anatomic differences between the patients, including short and muscled neck, small mandible with limited movements, fibrotic degenerations of cervical vertebrae related to age, anatomical defects of teeth, and small mouth with high arched palate.

The time to 25% T1 recovery is called the clinical duration of action. A study by Griffith et al. of 42 patients assigned to two groups found that in the group primed with of 0.06 mg/kg rocuronium, the clinical duration of action was 58 ± 22 minutes, whereas in the group with 0.6 mg/kg bolus rocuronium, it was 51 ± 20 minutes. Griffith et al. concluded that the priming technique did not extend the clinical duration of action.[11] Foldes et al. assigned 80 patients into two groups; the first group was given rocuronium 0.1 mg/kg and 0.5 mg/kg after four minutes, whereas the second group was given a single dose of rocuronium 0.6 mg/kg.[20] Clinical duration of action was 40 ± 3.2 minutes and 39.3 ± 2.4 in the priming group and single dose rocuronium group, respectively. The investigators concluded that priming had no impact on clinical duration of action.[20]

In this study, rocuronium priming was shown not to prolong clinical duration of action of rocuronium, as the clinical duration of action was similar in the rocuronium groups (Groups I and III). Similarly, there was no significant difference in the clinical duration of action in the vecuronium groups (Groups II and IV). There was no significant difference between total duration of action and recovery index in the vecuronium groups (Groups II and IV) and in the rocuronium groups (Groups I and III). These findings are compatible with other studies.[11,16,17]

In conclusion, findings of this study suggest that a priming with rocuronium in doses studied significantly reduces intubation time, provides perfect intubation conditions and is reliably useful, not only in situations where quick intubation is required but also in regular anesthesia practices.

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