

Retrospective Comparison of the Effects of Total Intravenous Anesthesia and Sevoflurane Anesthesia on the Clinical Duration of Action of Rocuronium in Diabetic and Non-Diabetic Patients: Retrospective Observational Study

Diyabetik ve Non-Diyabetik Hastalarda Total İntravenöz Anestezi ve Sevofluran Anestezisinin Rokuronyumun Klinik Etki Süresi Üzerine Olan Etkilerinin Retrospektif Olarak Karşılaştırılması: Retrospektif Gözlemsel Çalışma

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ABSTRACT Objective: Due to the decrease in nerve conduction velocity, the clinical effect of rocuronium may be prolonged in diabetic patients receiving inhalation anesthesia, and its postoperative residual muscle relaxant effect may lead to complications. We compared the effects of total intravenous anesthesia and sevoflurane anesthesia on the clinical duration of action of rocuronium in diabetic and non-diabetic patients. **Material and Methods:** Patients between the ages of 18-65, who underwent general anesthesia for elective surgery in the general surgery department of our hospital (0.6 mg of rocuronium was used for tracheal intubation), with Type 2 diabetes and with the American Society of Anesthesiologists Physical Condition Classification (ASA) I-II were included in the study. Non-diabetic patients (ASA I-II) of the same age were included in the study as the control group. The duration of the clinical effect of rocuronium between the time of administration of the first dose of rocuronium and the time of administration of the additional rocuronium dose (time recorded in TOFcount 2-TOFc2) was evaluated. **Results:** The clinical duration of action of rocuronium was longer in both diabetic groups than in non-diabetic groups ($p=0.000$). When the diabetic patient groups were compared, the clinical duration of action of rocuronium was longer in the diabetic sevoflurane group than in the diabetic group that received total intravenous anesthesia ($p=0.012$). **Conclusion:** It was determined that the duration of rocuronium action was longer in diabetic patients who were administered sevoflurane anesthesia than in patients who received total intravenous anesthesia and in non-diabetic patients.

ÖZET Amaç: İnhalasyon anestezisi alan diyabetik hastalarda, sinir iletim hızındaki azalma nedeniyle rokuronyumun klinik etkisi uzayabilmekte ve postoperatif rezidüel kas gevşetici etkisi komplikasyonlara neden olabilmektedir. Diyabetik ve diyabetik olmayan hastalarda total intravenöz anestezi ve sevofluran anestezisinin rokuronyumun klinik etki süresi üzerindeki etkilerini karşılaştırdık. **Gereç ve Yöntemler:** Hastanemiz genel cerrahi bölümünde, elektif cerrahi için genel anestezi uygulanan (trakeal entübasyon için 0,6 mg rokuronyum kullanılan) 18-65 yaşları arasında Tip 2 diyabetli, Amerikan Anesteziyologlar Derneği Fiziksel Durum Sınıflandırması [American Society of Anesthesiologists Physical Condition Classification (ASA)] II olan hastalar çalışmaya dâhil edildi. Aynı yaş aralıklı non-diyabetik hastalar (ASA I-II) kontrol grubu olarak çalışmaya dâhil edildi. İlk doz rokuronyum uygulama zamanı ile ek rokuronyum dozunun uygulama zamanı (TOFcount 2'de-TOFc2 kaydedilen süre) arasındaki rokuronyumun klinik etkisinin süresi değerlendirildi. **Bulgular:** Rokuronyumun klinik etki süresi her iki diyabetik grupta diyabetik olmayan gruplara göre daha uzun bulundu ($p=0,000$). Diyabetik hasta grupları karşılaştırıldığında, diyabetik sevofluran grubunda rokuronyumun klinik etki süresi diyabetik total intravenöz anestezi almış gruba göre daha uzundu ($p=0,012$). **Sonuç:** Sevofluran anestezisi uygulanan diyabetik hastalarda, rokuronyum etki süresinin total intravenöz anestezi uygulanan hastalara ve diyabetik olmayanlara göre daha uzun olduğu saptandı.

Keywords: Rocuronium; sevoflurane; diabetes mellitus; neuromuscular monitoring

Anahtar Kelimeler: Rokuronyum; sevofluran; diabetes mellitus; nöromusküler monitörizasyon

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The main components of general anesthesia include hypnosis, amnesia, analgesia and muscle relaxation. During an operation, muscle relaxation is absolutely necessary for endotracheal intubation to be more comfortable, more successful, less traumatic and easier to access to the surgical field. For this purpose, nondepolarizing type muscle relaxants are widely used in anesthesia practice. Among these muscle relaxants, rocuronium is the most preferred muscle relaxant drug because of its short duration of onset and its short duration of clinical effect.¹⁻³

It is known that inhalation anesthetics potentiate neuromuscular blockade of rocuronium.⁴

If intravenous anesthetics are used instead of inhalation anesthetics, it is known that there is no such potentializing effect.^{5,6}

It is unclear whether axonal destruction, demyelination and atrophy in the nerve muscle complex in patients Type 2 diabetes cause prolongation of clinical effects of non-depolarizing muscle relaxant drugs.^{7,8}

The aim of this study is: To compare the neuromuscular block characteristics of diabetic patients and non-diabetic patients under intravenous anesthetics and inhalation anesthetics retrospectively, based on the hypothesis that inhalation anesthetics may cause a clinical prolongation in neuromuscular block induced by rocuronium in diabetic patients as in other healthy patients.

MATERIAL AND METHODS

This study protocol was approved by the Ankara University Faculty of Medicine Clinical Research Ethics Committee (date: September 5, 2016, no: 14-664-16) and it conducted in accordance with the Declaration of Helsinki.

The study included patients with Type 2 diabetes and non-diabetic patients in American Society of Anesthesiologists (ASA) I-II physical class, who received rocuronium as a muscle relaxant at a dose of 0.6 mg kg⁻¹ for elective tracheal intubation. The patients underwent elective surgery in the general surgery operating rooms of our hospital between 01.04.2016-01.08.2016. All data were scanned

retrospectively from our hospital's electronic database and anesthesia follow-up forms.

Patients having neuromuscular, liver, kidney disease, patients on drugs known to interact with rocuronium (anticonvulsants, magnesium), patients with body-mass index <18.5 and >30 kgm⁻², and patients aged <18 years old were excluded from the study.

Twenty eight patients with Type 2 diabetes and 28 non-diabetic patients who met the study criteria were included in the study.

Patients were divided into 4 groups according to the type of anesthesia used and whether they were diabetic or not.

Group DT: Diabetic patients who have received total intravenous anesthesia (TIVA).

Group DS: Diabetic patients who received sevoflurane.

Group NDT: Non-diabetic patients who received TIVA.

Group NDS: Non-diabetic patients who received sevoflurane.

In addition to standard ASA monitoring all patients were monitored for depth of anesthesia with the Bispectral index (BIS) and the BIS value was between 40-60 in all patients as a standard of care of our institution.

In our hospital, neuromuscular monitoring (acceleromyography) is applied to all patients undergoing general anesthesia, and the ulnar nerve is preferred for this purpose (TOF -Watch®, Organon Ltd., Drynam Road, Swords, Co. Dublin, Ireland).

The duration of action of rocuronium is the time elapsed from rocuronium administration and TOF-c2 was obtained.

Data obtained from patient records included age, weight, height, anesthetic drugs and methods. Hemodynamic parameters (systolic, diastolic and mean blood pressures, heart rate, and oxygen saturation values) were recorded at baseline, at 5th, 10th and 20th minutes after intubation.

STATISTICAL ANALYSIS

The SPSS 24.0 package programme (SPSS Statistics for Windows, Version 24.0. IBM Corp., Armonk, NY, USA) was used to evaluate the data. Student's t, Mann-Whitney U, One-way, Kruskal-Wallis tests were used in comparisons. Results were accepted as $p < 0.05$ significant in 80% confidence interval. The study required a minimum of 36 patients for an 80% confidence interval. Fifty six patients were included in our study.

RESULTS

When the demographic characteristics of the patients were evaluated, it was found that each of the 4 groups were similar in terms of height, weight and sex. However, there was a statistically significant difference between the 4 groups in terms of age. When compared the patients included in the NDS and DS group the average age of the patients included in the NDS group was found to be lower than the average age of the patients in the DS group (Table 1). Similarly, when the NDT and DS groups were compared, the NDT group was found to be younger than the DS group (Table 1).

When the ASA physical status score was assessed, the scores of the diabetic patients were statistically significantly higher than the scores of the non-diabetic patients (Table 2).

There was no statistical difference in systolic blood pressure values between the groups.

There was a significant difference between the NDS and DT groups in terms of basal, diastolic blood pressures. Basal diastolic blood pressure was significantly lower in patients with DT group (Table 3).

The 10th minute diastolic blood pressure values after intubation were statistically lower in the DT group compared to the NDS group (Table 4). Also, diastolic blood pressure values obtained at the 20th minute after intubation were found to be statistically significantly lower in the DT group than in the NDS group (Table 3).

There was no statistical difference in mean blood pressure values between the groups. There was no significant difference between groups according to heart rate.

TABLE 1: Comparison of groups in terms of age.

	NDS	DS	NDT	DS	p value**
Age (year)	47.21±13.29	67.9±12.50	48.19±12.50	67.9±12.50	0.001

** $p < 0.05$ statistically significant difference. Data are given as mean±standart deviation; NDS-non-diabetic sevoflurane group; DS-diabetic sevoflurane group; NDT-non-diabetic TIVA group.

TABLE 2: Comparison of groups in terms of ASA score.

		NDS	NDT	DS	DT	p value**
ASA	I (n, %)	7, 50%	9, 64.3%	0, 0.0%	0, 0.0%	0.000
	II (n, %)	7, 50%	5, 35.7%	14, 100.0%	14, 100.0%	

** $p < 0.001$ statistically highly significant difference between diabetic and non-diabetic groups. Data are given as mean±standart deviation; ASA: The American Society of Anesthesiologists physical status classification; NDS: Non-diabetic sevoflurane group; NDT: Non-diabetic TIVA group; DS: Diabetic sevoflurane group; DT: Diabetic TIVA group.

TABLE 3: Comparison of diastolic blood pressure between groups.

DBP (mmHg)	NDS	DT	p value*
Basal	86.00±10.33	73.43±11.91	0.022
10 th minute after intubation	75.64±15.75	58.93±11.19	0.012
20 th minute after intubation	73.21±16.19	63.86 ±13.31	0.011

* $p < 0.05$ statistically significant difference. Data are given as mean±standart deviation; DBP: Diastolic blood pressure; NDS: Non-diabetic sevoflurane group; DT: Diabetic TIVA group.

TABLE 4: Comparison of TOFc2 values between groups.

	NDS	NDT	DS	DT
TOFc2 (min)	33.93±2.27 ^a	35.43±2.56 ^c	45.57±1.91 ^d	42.57±2.56 ^b
	p=0.000	p=0.000	p=0.012	p=0.000

^ap<0.001, statistically highly significant between NDS and DS groups; ^bp<0.001, statistically highly significant between NDS and DT groups; ^cp<0.001, statistically highly significant between NDT and DT groups; ^dp<0.05, statistically significant difference between DT and DS groups; TOFc2: Train-of-4 counts (count 2); NDS: Non-diabetic sevoflurane group; NDT: Non-diabetic TIVA group; DS: Diabetic sevoflurane group; DT: Diabetic TIVA group.

Peripheral oxygen saturation values were not significantly different between the groups.

When we compare groups in terms of the duration of clinical effect of rocuronium; the mean duration in non-diabetic group (NDS) was 33.93±2.27 min (NDT 35.43±2.56 min). In the diabetic group (DS), this time was 45.57±1.91 minutes (DT 42.57±2.56 min) and there was a statistically significant difference between the group 2 groups (p<0.01).

It was seen that the time to reach TOFc2 was longer in both diabetic groups than in non-diabetic groups. Highly significant differences were found between groups (Table 4). Comparing the diabetic patient groups, it was seen that the time to reach TOFc2 value in the DS group (45.57±1.91) was longer than the DT group (42.57±2.56) (p=0.012).

DISCUSSION

Diabetes mellitus is a chronic metabolic disease that affects many systems with various clinical and biochemical findings. Hyperglycaemia leads to various complications (macrovascular, microvascular). High blood sugar levels cause osmotic diuresis, resulting in polyuria, nocturia, thirst, fatigue and weight loss. Type 2 diabetes mellitus is a slow-growing disease characterized by peripheral insulin insensitivity, usually of genetic origin, occurring in adult age. Approximately 80% of all diabetic patients are obese.

There is a growing population of Type 2 diabetic patients scheduled for surgery for different reasons. Knowing the diagnosis, treatment and complications of this disease facilitates patient management in the perioperative period. In this study, the effects of total intravenous anesthesia and sevoflurane anesthesia on

the duration of clinical effect of rocuronium in diabetic and non-diabetic patients were compared. The duration of clinical effect of rocuronium is significantly longer in diabetic patients compared to non-diabetics.⁹

In addition, it has been found sevoflurane in diabetic patients leads to prolongation of the clinical effect of rocuronium compared to total intravenous anesthesia.¹⁰

In diabetic patients, impairment of function of motor nerve fibers and damage to nerve endings may occur.^{7,11} Histopathologic studies have shown that neuropathy develops due to axonal loss and segmental demyelination.¹¹ The most frequently affected peripheral nerves are median, ulnar, radial and femoral nerves respectively.¹² In addition to neuropathy, musculoskeletal atrophy and infarction are common complications in diabetic patients.¹³

In long-term hyperglycemia (as the duration of the disease increases), changes in the nerves are more common.¹⁴

In diabetes mellitus, the early detection and prevention of these complications is as important as the treatment of the disease itself.

In the literature, there are studies on biomarkers of diabetic complications (especially diabetic peripheral neuropathies) (glycosylated hemoglobin-HbA1c, tumor necrosis factor alpha-tumor necrosis factor-alpha, glyoxalase I-GLO I, adiponectin).¹⁵⁻¹⁷

Since our study was retrospective, biomarkers could not be evaluated in our patients.

It is thought that prolongation of the clinical effect of rocuronium may be related to prejunctional and postjunctional pathological changes occurring in diabetic patients.^{18,19} In this study we have

demonstrated that the duration of clinical effects of rocuronium in diabetic patients is both statistically and clinically prolonged, compared to non-diabetic patients, independently of anesthesia technique. We know that the recovery time of non-depolarizing muscle relaxants is prolonged in diabetic patients.¹⁹ In another study it was seen that sevoflurane causes significant prolongation in the clinical effect of vecuronium compared to total intravenous anesthesia in diabetic and non-diabetic patients.⁴ In this study we have shown that diabetes increases the duration of the clinical effect of rocuronium as in vecuronium.

Therefore, attention should be paid to the prolongation of the clinical effects of nondepolarizing neuromuscular blockers used in diabetic patients.

Volatile anesthetics frequently used in anesthesia management are generally thought to potentiate the effects of neuromuscular blockers through 3 mechanisms (central motor neuron effect, increased receptor affinity of muscle relaxant drug, or inhibition of postsynaptic acetylcholine receptors). Although there was no significant difference between the NDS and NDT groups in our study, there was a significant difference between the DS and DT groups in terms of the duration of clinical effects of rocuronium ($p < 0.05$). Although we did not investigate total rocuronium dose applied during surgery, it is clear that volatile agents reduce the nondepolarizing muscle relaxant requirement by at least 15%. Volatile anesthetics potentiate the effects of muscle relaxants and reduce the need for additional dose, prolong the duration of the muscle relaxant effect and recovery time. Volatile anesthetics do not affect the onset of action of neuromuscular blockers, but prolong the duration of clinical effect and recovery time. Intravenous anesthetics do not have this potentiating effect.²⁰⁻²²

The clearance of rocuronium is mostly by hepatobiliary and renal route, and damage to these organs is responsible for the prolonged effect of rocuronium. In our study, the duration of clinical effect of rocuronium at the induction dose was investigated and it was clear that prolonged effect was not related to clearance since liver and kidney functions were normal in patients.

Pühringer et al. compared obese and normal body-weighted patients and found that the onset time of rocuronium was shorter in obese patients and the duration of clinical effect was similar.²³

In our study, there was no significant difference between the groups in terms of weight, but in terms of age, it was observed that elderly patient population was more in diabetic group. Age has an effect on drug pharmacokinetics. The duration of action of rocuronium is longer in the geriatric population.^{24,25} There are reports that the onset of neuromuscular block may be delayed in elderly patients and this delay may be correlated with age.^{24,25} Lee et al. stated that this age related effect, may be caused by the decrease in cardiac output and prolongation of the circulation time.²⁶

Varrique et al. in their study, an increase in aurodose (area under the curve) and reduced volume of distribution of rocuronium were observed in the elderly patient population. At the same time, there is a decrease in the need for rocuronium due to the decrease in renal clearance.²⁷

In our study, the mean age of the diabetic group is greater than that of the non-diabetic group and this age factor may play a role in the prolongation of the clinical effect of rocuronium in the diabetic group.

LIMITATIONS

One of the disadvantages of our study is that it is retrospective. Parameters such as duration of disease in diabetic patients, fasting blood sugar and glycosylated hemoglobin values were not included in the study. During TOF monitoring, the resistance of the skin and the factors affecting it (skin temperature, adequacy of electrode application) could not be evaluated.

CONCLUSION

Diabetes mellitus is a chronic metabolic disease with various clinical and biochemical findings that can affect many systems. In diabetic patients, the function of motor nerve fibers may be impaired and nerve endings may be damaged. In histopathological studies, it has been shown that neuropathy occurs due to axon loss and segmental demyelination.

Consequently, it is thought that prolongation of the clinical effect of rocuronium may occur in diabetic patients due to pathological changes at the neuromuscular junction.

In this study we conducted, we demonstrated that the duration of clinical action of rocuronium was prolonged both statistically and clinically in diabetic patients compared to non-diabetic patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Dostali Aliyev, Sacide Demiralp; **Design:** Dostali Aliyev, Sacide Demiralp; **Control/Supervision:** Dostali Aliyev, Sacide Demiralp; **Data Collection and/or Processing:** Dostali Aliyev, Sacide Demiralp; **Analysis and/or Interpretation:** Dostali Aliyev, Sacide Demiralp, Tuğba Mert; **Literature Review:** Dostali Aliyev; **Writing the Article:** Dostali Aliyev; **Critical Review:** Dostali Aliyev, Sacide Demiralp.

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