

Bilateral Non-Reactive Fixed and Dilated Pupils Caused by Rocuronium and Successfully Reversed with Sugammadex: A Case Report and Literature Review

Suggamadeks ile Başarılı Revers Edilen Rokuronyuma Bağlı Bilateral Nonreaktif Fiks Dilate Pupil: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

^{ib} Pınar KARABACAK^a, ^{ib} Onurcan BALIK^a, ^{ib} Oya KURUŞCU^a, ^{ib} Mustafa Soner ÖZCAN^a,
^{ib} Eyyüp Sabri ÖZDEN^a

^aDepartment of Anesthesiology and Reanimation, Süleyman Demirel University Faculty of Medicine, Isparta, Türkiye

ABSTRACT Coronavirus disease-2019 (COVID-19) is a serious infectious disease, which may cause various clinical conditions ranging from asymptomatic cases to severe complications like acute respiratory distress syndrome (ARDS) and even to death. Although there are some differences between COVID-19-associated ARDS and conventional ARDS, mortality is still high. Infusion of a non-depolarizing muscle relaxant is recommended in ARDS patients with a PaO₂/FiO₂ ratio <100. Rocuronium is a non-depolarizing muscle relaxant, which cannot cross the blood-brain barrier. Therefore, side effects related to the central nervous system are not expected. However, rocuronium may penetrate the central nervous system in patients with disrupted blood-brain barrier and there are a few case reports in the literature with rocuronium-associated fixed and dilated non-reactive pupils. This is a very rare condition. In this case report, we present a COVID-19 patient, who had bilateral dilated and non-reactive pupils that was related to rocuronium infusion and reversed with sugammadex.

Keywords: Rocuronium; sugammadex; COVID-19

ÖZET Koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] asemptomatik olgulardan akut solunum sıkıntısı sendromu [acute respiratory distress syndrome (ARDS)] gibi ciddi komplikasyonlara hatta ölüme neden olabilen ciddi bir enfeksiyon hastalığıdır. COVID ARDS'inde (CARDS) normal ARDS den farklılıklar olsa da mortalitesi hala yüksektir. Nondepolarizan kas gevşetici infüzyonu, PaO₂/FiO₂ oranı<100 olan ARDS hastalarında önerilen bir tedavidir. Rokuronyum kan beyin bariyerini geçmeyen bir non depolarizan kas gevşetici ajandır. Bu nedenle santral yan etkilerin görülmesi beklenmez. Kan beyin bariyerinin bozulduğu klinik durumlarda rokuronyumun santral sinir sistemine geçişinin kolaylaşması sonucu fix ve dilate nonreaktif pupilin görülebildiği çok az sayıda olgu sunumunda bildirilmiştir. Oldukça nadir görülen bir durumdur. Burada, rokuronyum infüzyonuna bağlı, bilateral dilate ve non reaktif pupil gözlenen ve suggamadeks ile revers edilen Covid 19 hastası sunulmuştur.

Anahtar Kelimeler: Rokuronyum; suggamadeks, COVID-19

Coronavirus disease-2019 (COVID-19) is a serious viral infection, which may cause various clinical conditions ranging from mild-to-moderate symptoms to fatal consequences.¹

Rocuronium is a neuromuscular blocking agent (NMBA). It is widely used in general anesthesia and also recommended as an infusion therapy in patients with acute respiratory distress syndrome (ARDS),

who require intensive respiratory support.² Although fixed and dilated pupils were mentioned in a few case reports, it was considered as not a very frequent side effect of rocuronium.^{3,4} In this case report, we presented a patient, who was treated with rocuronium infusion due to the COVID-19 related ARDS and developed bilateral fixed and dilated pupils.

Correspondence: Pınar KARABACAK

Department of Anesthesiology and Reanimation, Süleyman Demirel University Faculty of Medicine, Isparta, Türkiye

E-mail: drpinara@gmail.com



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CASE REPORT

The 31-year old female patient, who was treated due to COVID-19 related pneumonia in another health center, was transferred to the intensive care unit (ICU) after developing hypoxemia and tachypnea. The patient did not have any co-morbidity and was pregnant at admission (29w6d). The Glasgow Coma Scale value was 15 points. During admission, the patient was on the 14th day of COVID-19 diagnosis and it was found out that she was not vaccinated for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). During the ultrasonographic examination, no fetal heartbeat and fetal movements were observed. As a result of the diagnosis of the intrauterine fetal death, pregnancy was terminated with normal spontaneous vaginal delivery in the clinic of gynecology and obstetrics. As hypoxemia persisted, a high-flow nasal oxygen supply was initiated. Furthermore, thromboprophylaxis and steroid treatment were also initiated. As the patient had fever, empirical treatment with meropenem and teicoplanin was also added to the treatment. On the 2nd day in ICU, endotracheal intubation was carried out, who had ARDS in high-resolution computed tomography examination and mechanical ventilation was initiated. Rocuronium infusion, a NMBA, was started in the patient with severe hypoxemia ($\text{PaO}_2/\text{FiO}_2 < 100$) despite sedation on the 10th day of hospitalization to optimize oxygenation. The depth of the neuromuscular relaxation was monitored with the help of clinical signs and the dose of rocuronium was titrated between 4 and 20 mg/h. The clinical evaluation included signs of ventilatory effort, ventilator incompatibility, high peak airway pressure, and observation of the inspiratory triggering of the ventilator. Forty hours after the rocuronium infusion, we observed bilateral dilated (8 mm) non-reactive pupils in the patient. The patient didn't receive any medication that caused pupillary dilatation or increase rocuronium's effects. The neurological examination was performed under sedation. The neurological examination was consistent with brain death but it was considered not significant as the patient was under sedation. In order to exclude intracranial pathologies and brain death, brain

computed tomography and transcranial Doppler examination were carried out, which did not reveal any pathological findings. As the clinical condition might depend on the rocuronium infusion, the infusion was stopped and 200 mg sugammadex was administered as an antidote. The bilateral pupil size became gradually smaller following the injection. After 5 hours of the sugammadex injection, the patient's pupils returned to their normal size and the patient began to respond to the verbal stimuli with specific extremity movements. Another NMBA wasn't used for hypoxemia. During follow-up, hypoxia increased although she was on mechanical ventilation and died due to ARDS on the 28th day of admission. Informed consent was obtained from the patient's family.

DISCUSSION

COVID-19 killed millions of people since the start of the pandemic.¹ The infusion of NMBAs is recommended in patients with $\text{PaO}_2/\text{FiO}_2 < 100$. It was demonstrated that oxygenation is improved with compatible mechanical ventilation.^{1,5} Although general anesthesia and muscle relaxation for intubation are the main areas of usage, it was recommended also in hypoxia caused by ARDS (severe ARDS with $\text{PaO}_2/\text{FiO}_2 < 100$) up to 48 hours.¹ Although it does not cross the blood-brain barrier and does not affect the central nervous system, it was shown that it might pass the blood-brain barrier if the blood-brain barrier is disrupted or immature.⁴ Mydriasis is not an expected finding in rocuronium use. Regarding the literature, it was reported that rocuronium might cause voluntary mydriasis after local application to the eye in animals.⁶ It was reported that mydriasis might occur particularly in newborns with immature blood-brain barrier (BBB), in patients with disrupted BBB caused by infection and certain treatments, or after the administration of high dose rocuronium.⁷ Regarding the literature, non-reactive and dilated pupils were first reported in 2000, who received muscle relaxant infusion over 3 days.⁸ Bilateral non-reactive mydriasis was developed in a newborn, who received 4 doses of rocuronium in intervals during the anesthesia.⁷ Although rocuronium does not cross BBB, it was detected in

the cerebrospinal fluid in a patient, who underwent cerebral aneurysm surgery.⁹ Neurological complications are common in COVID-19. Although SARS-CoV-2 was detected in the brain tissue of patients, the mechanism of the penetration and outcomes were not fully elucidated.¹⁰ Several complications in COVID-19 leading to death are cytokine-mediated. The term “cytokine storm”, which became popular with COVID-19, was the precursor of many clinical outcomes. It was reported that patients infected with coronavirus 2 (SARS-CoV-2) and who had severe ARDS showed encephalopathy and neuro-inflammation originating from the cytokine storm.¹¹ Therefore, it is not much of a surprise that rocuronium, which does not cross BBB, can cause these findings in COVID-19 patients. There are 2 papers in the literature focused on rocuronium-associated fixed and dilated pupils in COVID-19 patients. In the first paper, Zakyntinos et al. reported a case series consisting of 3 patients. All patients received rocuronium infusion due to ARDS and all developed fixed and dilated non-reactive pupils and pupils responded to the light reflex normally after the discontinuation of the drug. Sugammadex was not administered as an antidote.⁴ The second paper was a case report focused on a 34-year old COVID-19-associated ARDS patient, who received rocuronium infusion and developed rocuronium-associated non-reactive pupils. After the observation of this finding, rocuronium infusion was terminated and the pupil size and reactions returned to normal approximately after 12 hours.¹² Sugammadex is a newly developed pharmacological agent to reverse the neuromuscular blockade. It forms stable complexes with steroidal NMBAs, particularly with rocuronium. It is thought that it does not cross the blood-brain barrier. However, if BBB's integrity is disrupted, rocuronium may pass the barrier. Sugammadex may reduce or reverse rocuronium's effects by decreasing its plasma levels. The blood-brain barrier reduced the penetration (in rats <3%) and therefore toxic effects on the central nervous system

were not expected.¹³ Sugammadex may be also used to reverse the symptoms related to the central nervous system. Considering the literature, the dilated and fixed pupils, which emerged following the rocuronium infusion, were reversed effectively with sugammadex, the pupil's size became normal, and the patient was successfully awakened.³ In other case reports found in the literature, sugammadex was not used, only drug treatment was stopped, and pupils returned to the normal size gradually in all patients.

In conclusion, non-reactive or dilated pupils in patients under sedation are an important concern to clinicians. It may be a precursor of a serious intracranial event. Rocuronium-associated fixed and dilated pupils are an unexpected and rare complication of rocuronium infusion. In cases of fixed and dilated non-reactive pupils, possible intracranial causes should be definitively excluded and it should be kept in mind that it may be associated with a NMBA like rocuronium.

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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: Pinar Karabacak, Onurcan Balık; **Design:** Pinar Karabacak; **Control/Supervision:** Eyyüp Sabri Özden; **Data Collection and/or Processing:** Oya Kuşçu, Onurcan Balık; **Analysis and/or Interpretation:** Pinar Karabacak; **Literature Review:** Pinar Karabacak, Mustafa Soner Özcan; **Writing the Article:** Pinar Karabacak.

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