Brazilian Journal of Anesthesiology 2022;72(6): 829—831

Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

SHORT COMMUNICATION

Non-reactive mydriasis after rocuronium infusion in patients with COVID-19: a case series

Flávia Assis Fernandes [a], João Paulo Jordão Pontes [a,b,*], Celso Eduardo Rezende Borges [b], Erika Lopes Honorato [c], Sanzio Dupim Soares [d], Norma Sueli Pinheiro Módolo [e], Laís Helena Navarro e Lima [e,f]

[a] *Hospital Mater Dei Santa Genoveva de Uberlândia, Departamento de Anestesiologia, Uberlândia, MG, Brazil*
[b] *Uberlândia Medical Center, Departamento de Anestesiologia, Uberlândia, MG, Brazil*
[c] *Uberlândia Medical Center, Departamento de Neurologia, Uberlândia, Uberlândia, MG, Brazil*
[d] *Uberlândia Medical Center, Departamento de Terapia Intensiva, Uberlândia, MG, Brazil*
[e] *Universidade Estadual Paulista (UNESP), Departamento de Anestesiologia, Botucatu, SP, Brazil*
[f] *Queens University, Department of Anesthesia and Perioperative Care, Kingston, Canada*

Received 18 February 2022; accepted 28 May 2022
Available online 8 June 2022

Introduction

The routine use of Neuromuscular Blocking Agents (NMBAs) in patients under mechanical ventilation due to Acute Respiratory Distress Syndrome (ARDS) still causes debate. Although NMBA infusion improves oxygenation in moderately severe ARDS, its effect on mortality is contentious, as most studies have assessed infusions of only 48-hour duration and with cisatracurium.[1] Currently, 88% of patients with Coronavirus Disease 2019 (COVID-19)-related ARDS under mechanical ventilation need an NMBA infusion to optimize oxygenation and ventilation. In contrast, only 22% of patients with "classic ARDS" need an NMBA for the same purpose.[2]

NMBAs are hydrophilic polar molecules that cannot normally cross the Blood-Brain Barrier (BBB).[3] However, NMBAs can impair cholinergic transmission in the Central Nervous System (CNS), producing autonomic dysfunction, excitotoxicity, seizures, and neuronal death, when the BBB becomes permeable due to pathological conditions.[3] Accordingly, mydriasis has been reported due to prolonged NMBA infusions in patients with disrupted BBB caused by severe systemic inflammation,[4] and in patients with immature BBB function.[5,6] Causes of mydriasis include parasympathetic nervous system block, sympathetic nervous system hyperstimulation, cerebral vascular injuries, and brain death.[7]

Non-reactive dilated pupils might represent an important warning sign for neurological complications, especially in unconscious mechanically ventilated patients when a more comprehensive neurological physical exam might not be possible. After obtaining written consent from patients or patients' relatives for reporting and publication, we describe three cases of mechanically ventilated COVID-19 patients with mydriasis who received continuous rocuronium infusion for respiratory parameter optimization.

Case 1

A previously hypertensive 50-kg, 65-year-old female patient (former smoker) was admitted to an Intensive Care Unit (ICU) with respiratory failure due to COVID-19 and underwent orotracheal intubation after 17 days of symptoms. The patient was sedated with ketamine 0.2 $mg.kg^{-1}.h^{-1}$, fentanyl 50 $mcg.h^{-1}$, and midazolam 5 $mg.h^{-1}$. A continuous infusion of rocuronium (15 $mg.h^{-1}$) was started due to

* Corresponding author.
E-mail: pontesjpj@gmail.com (J.P. Pontes).

https://doi.org/10.1016/j.bjane.2022.05.007

ventilator asynchrony after 1-week of mechanical ventilation. She presented with fixed mydriasis not responding to light after 48 h of rocuronium infusion. Laboratory tests did not show any changes that could justify the change in the pupillary pattern. Likewise, no structural changes were observed on Computed Tomography (CT) of the head. Rocuronium was discontinued, leading to complete regression of the pupillary pattern 24 h after the discontinuation. The patient was discharged from the hospital without neurological sequelae 42 days after the fixed mydriasis episode.

Case 2

A 69-kg, 71-year-old male patient with a history of hypertension, diabetes, and dementia was admitted to an ICU with respiratory failure due to COVID-19 and intubated 12 days after the onset of symptoms. He was sedated with ketamine 0.2 $mg.kg^{-1}.h^{-1}$, propofol $mg.kg^{-1}.h^{-1}$, and dexmedetomidine 0.5 $mcg.kg^{-1}.h^{-1}$. Continuous infusion of 20 $mg.h^{-1}$ rocuronium was started after 3 days of tracheal intubation to improve ventilator synchrony. Bilateral mydriasis was observed in 48 h. Laboratory tests showed anemia, elevated inflammatory markers, and acute renal failure (serum creatinine: 1.8 $mg.dL^{-1}$). An urgent head CT scan showed no structural changes. Due to the suspicion of rocuronium-induced mydriasis, the drug was discontinued. In 12 h, an isochoric, medium, and reactive pupillary pattern was observed. Although the patient regained consciousness 1 week after the mydriasis episode, he died 9 days later due to sepsis caused by bacterial pneumonia.

Case 3

A previously hypertensive 95-kg, 49-year-old male patient was admitted to an ICU with respiratory failure due to COVID-19 and intubated 10 days after the onset of symptoms. The patient was receiving ketamine 0.3 $mg.kg^{-1}.h^{-1}$, midazolam 5 $mg.h^{-1}$, fentanyl 2 $mcg.kg^{-1}.h^{-1}$, and rocuronium 25 $mg.h^{-1}$ in a continuous infusion. Anisocoria, followed by fixed 7-mm mydriasis, developed in 48 h after rocuronium infusion (Fig. 1; Supplemental Video 1). A head CT scan was unremarkable. Clinical measures for neuroprotection were initiated. Clinically, the patient had non-dialytic acute renal failure (serum creatinine: 3.7 $mg.dL^{-1}$) without electrolyte disturbances. Therefore, rocuronium-induced mydriasis was suspected. The pupillary pattern returned to normal after 36 h of rocuronium infusion discontinuation. The patient died 5 days after the mydriasis episode due to sepsis caused by bacterial pneumonia.

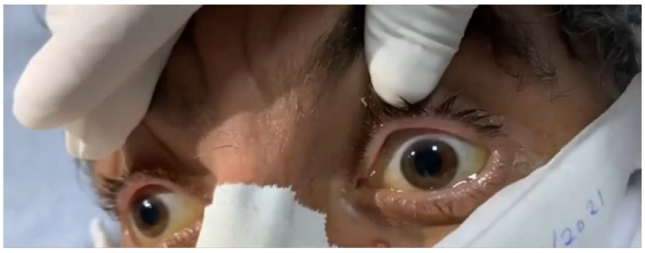

Figure 1 Anisocoric pupils after continuous rocuronium infusion.

In all three cases, the patients received antibiotic therapy, daily dexamethasone, and thromboprophylaxis with therapeutic doses of enoxaparin.

Discussion

In addition to being a hydrophilic molecule, rocuronium has a molecular weight of 610 Da, exceeding the normal permeability limit of the BBB of 450 Da.[6] However, situations of BBB integrity loss can facilitate the access of rocuronium to the CNS.[8] COVID-19 is associated with the release of a storm of pro-inflammatory cytokines, generating systemic inflammation and increased endothelial permeability. The spike protein of SARS-CoV-2 can destabilize the BBB by reducing tight-junction resistance and expression of metalloproteinases that ultimately facilitate neuroinflammation and might be the explanation for the neurological manifestations after COVID-19.[9] The three patients mentioned in this report had severe systemic manifestations with a high probability of affecting the BBB integrity, which would facilitate the effects of rocuronium on the CNS.

Fixed mydriasis episodes have already been reported in neonates after high doses of rocuronium,[5,6] suggesting the passage of the drug to the CNS due to the immaturity of the BBB. Fixed mydriasis has also been reported in patients with ARDS undergoing Extracorporeal Membrane Oxygenation (ECMO) therapy under continuous infusion of rocuronium.[4] NMBAs can act as antagonists in different cerebral nicotinic receptors despite an association among NMBA excitatory effects, such as seizures, due to the increase in intracellular calcium.[3] Therefore, drugs with anticholinergic effects might present paradoxical CNS effects, depending on the agent, concentration, and subtype of the respective receptor.[8] The pupillary diameter at rest represents a balance between the two systems: stimulation of the Sympathetic autonomic Nervous System (SNS) dilates the pupil, and Parasympathetic autonomic Nervous System (PNS) stimulation contracts it. Therefore, SNS activation or PNS inhibition causes mydriasis.[7] Furthermore, other factors, such as local or systemic administration of medications, can change pupil diameter.[7] Regarding the autonomic balance of the pupillary reflex, NMBAs seem to preferentially inhibit cholinergic transmission, causing mydriasis.[4-6,8]

Upon sudden-onset fixed mydriasis in comatose patients, the diagnosis causing this sign should be promptly investigated, as it is generally a life-threatening sign.[7] Therefore, CNS insults, such as cerebral edema, brainstem ischemia/infarction, or hemorrhage, must be immediately recognized and treated. Arterial and venous thrombosis is a common manifestation in patients with COVID-19, requiring antithrombotic prophylaxis. Nevertheless, this approach is not without risks since hemorrhagic complications, including bleeding into the CNS, might occur. All patients in this report were immediately assessed with a head CT to rule out structural causes amenable to surgical or clinical treatment. Additionally, causes such as pharmacological PNS inhibition (i.e., with atropine), excessive sympathetic activity (overdose of sympathomimetics or high doses of vasoactive amines), hypothermia, barbiturate overdose, and hypermagnesemia, among other causes, should also be ruled out.[7] The patients in this report were normothermic and were not

using vasoactive sympathomimetic amines at mydriasis presentation. Furthermore, they were neither receiving antimuscarinic drugs nor had electrolyte disturbances. Ketamine infusion has been associated with bilateral light-responsive mydriasis; however, when given in higher doses than our patients received and in repeated bolus.[10] Moreover, all our patients presented with a fixed mydriasis pattern, which differs from the pattern of ketamine.

In line with other case reports,[4,5] the time association between rocuronium suspension and pupillary reflex recovery, in addition to the evidence in animal experiments,[3] indicate the CNS effect of this drug. Additionally, Langley et al.[6] demonstrated reversal of mydriasis in neonates submitted to anesthesia with rocuronium immediately after the infusion of sugammadex, a specific reversal agent of this NMBA. In all cases, the patients had been on high doses of rocuronium in continuous infusion and had some reason for loss of integrity of the BBB in common.[4-6] Another important point refers to the probably higher rocuronium plasma level in patients 2 and 3 owing to altered creatinine clearance. Interestingly, similar case reports with other nondepolarizing NMBAs, such as atracurium and vecuronium, suggest a "pharmacological class" mydriatic effect in patients with impaired BBB.[8]

In summary, a mydriatic and hyporesponsive pupillary pattern is associated with poor neurological prognosis. Therefore, knowing the medications that can interfere with or even mimic neurological injury is essential for the adequate management of critically ill patients. Thus, continuous rocuronium infusion should be considered as a differential diagnosis in a patient who develops bilateral fixed mydriasis simultaneous to widespread NMBA use due to the COVID-19 pandemic.

Conflicts of interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjane.2022.05.007.

References

1. Welhengama C, Hall A, Hunter JM. Neuromuscular blocking drugs in the critically ill. BJA Educ. 2021;21:258—63.
2. Grasselli G, Cattaneo E, Florio G, et al. Mechanical ventilation parameters in critically ill COVID-19 patients: a scoping review. Crit Care. 2021;25:115.
3. Cardone C, Szenohradszky J, Yost S, et al. Activation of brain acetylcholine receptors by neuromuscular blocking drugs. A possible mechanism of neurotoxicity. Anesthesiology. 1994;80:1155—61. discussion 29A.
4. He H, Yu Z, Zhang J, et al. Bilateral dilated nonreactive pupils secondary to rocuronium infusion in an ARDS patient treated with ECMO therapy: a case report. Med (Baltim). 2020;99:e21819.
5. Joyce C, Greenwald BM, Han P. Bilateral dilated nonreactive pupils in a neonate after surgery. A A Case Rep. 2016;6:286—7.
6. Langley RJ, McFadzean J, McCormack J. The presumed central nervous system effects of rocuronium in a neonate and its reversal with sugammadex. Paediatr Anaesth. 2016;26:109—11.
7. Thomas PD. The differential diagnosis of fixed dilated pupils: a case report and review. *Crit* Care Resusc. 2000;2:34—7.
8. Schmidt JE, Tamburro RF, Hoffman GM. Dilated nonreactive pupils secondary to neuromuscular blockade. Anesthesiology. 2000;92:1476—80.
9. Buzhdygan TP, DeOre BJ, Baldwin-Leclair A, et al. The SARS-CoV-2 spike protein alters barrier function in 2D static and 3D microfluidic in-vitro models of the human blood—brain barrier. Neurobiol Dis. 2020;146:105131.
10. Vide S, Costa CM, Gambus PL, et al. Effects of ketamine on pupillary reflex dilation: a case report. A A Pract. 2018;10:39—41.