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Fixed dilated pupils in Covid-19 ARDS patients under rocuronium, reversed after discontinuation

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ABSTRACT

Neuromuscular Blockade Agents (NMBA) are used in the management of moderate and severe Acute Respiratory Distress Syndrome (ARDS) patients. They have never been reported to present Central Nervous System adverse reactions. Shortage of cis-atracurium during the pandemic, led to the use of rocuronium. We report three patients with Covid-19 ARDS, who presented bilateral dilated, non-reactive pupils, after continuous rocuronium infusion. Brain CT findings were unremarkable and transcranial doppler tracings did not suggest brain edema or hemorrhage. NMBA's discontinuation led to reversal of the pupillary dilation. We believe that impairment of Blood-Brain-Barrier, due to Covid-19, led rocuronium access into the Central Nervous System, leading to this adverse effect. Clinicians should be aware of this adverse reaction when managing patients with Covid-19 ARDS warranting NMBA use.

1. Introduction

Neuromuscular Blockade Agents (NMBA) are used in the management of moderate and severe Acute Respiratory Distress Syndrome (ARDS) patients to alleviate patient-ventilator dyssynchrony, abolish spontaneous respiratory efforts (decreasing work of breathing, relaxing respiratory muscles and reducing oxygen consumption), and facilitating lung protective ventilation [1]. During the last year, Covid-19 ARDS patients have overwhelmed Intensive Care Units (ICU). NMBA have been extensively used during the pandemic [2]. Prolonged continuous administration may result in high NMBA concentrations.

Covid-19 has been reported to implicate the Central Nervous System as well, and disruption of Blood-Brain Barrier (BBB) may be present in such conditions [3]. NMBA do not cross intact BBB, but in case of BBB dysregulation and high NMBA concentrations, central effects could be induced.

In our institution, neuromuscular-blocking agents in continuous infusion were administered to Covid-19 ARDS patients, in accordance with guidelines [1]. Rocuronium was used in some cases due to a shortage of cis-atracurium. Pupillary reflexes were closely monitored to assess neurologic changes, due to the high thrombotic risk in these patients and enhanced thromboprophylaxis used. Dilated nonreactive pupils are commonly associated with profound Central Nervous System pathology. We report three patients with Covid-19 ARDS who presented bilateral dilated, non-reactive pupils, after continuous rocuronium infusion. The patients had no obvious brain damage and the condition was reversed with drug cessation.

2. Case series

Three patients, 2 males and 1 female, were hospitalized for Covid-19 ARDS. They were intubated and mechanically ventilated, under sedation with continuous infusion of propofol, midazolam and remifentanil, and warranted a low noradrenaline dosage to maintain adequate perfusion. To optimize oxygenation, NMBA using rocuronium was initiated, titrated at a dose range of 4-20 mg/h, according to the patients' response on triggering the ventilator. After 8, 56 and 126 h of rocuronium initiation, the patients presented bilateral, dilated, non-reacting pupils. All patients were treated with Remdesivir and enhanced thromboprophylaxis.

The first patient was a 56-year-old male, with no underlying comorbidities, and presented dilated (7 mm) non-reactive pupils after 56 h of continuous rocuronium infusion. In order to exclude brain edema, brain stem infarction or hemorrhage, a brain computed tomography (CT) with angiography was performed. WResults were unremarkable. Transcranial Doppler revealed normal cerebral blood flows. No other agent which could induce pupillary dilation was administered, so we hypothesized that rocuronium was responsible for this side effect. Five hours after the agent was discontinued, the pupils gradually returned to normal (2 mm) and became reactant the next day. The patient had normal renal function [creatinine 0.68 mg/dl, estimated Glomerular Filtration Rate (eGFR) 120 ml/min/m^2]. On the 12th ICU day, the patient was weaned from the ventilator, with normal consciousness and no neurological deficit. Four days after ICU discharge, he was readmitted for respiratory distress due to Hospital Acquired Pneumonia ARDS. Re-evaluation for SARS-Cov-2 was negative (twenty-five days post symptom onset). He was intubated and sedated, also receiving a continuous rocuronium infusion. Twelve hours later, pupillary dilation reappeared

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(8 mm), which was reversed with rocuronium discontinuation, strengthening the agent's causative relationship to the phenomenon.

The second patient presented dilated (8 mm), non-reactive pupils, after 8 h of rocuronium infusion (creatinine 3.31 mg/dl, eGFR 13.5 ml/min/m^2). Due to severely compromised oxygenation status, brain CT was not performed, but transcranial doppler ultrasonography did not reveal signs of intracranial hypertension, although normal cerebral blood flow was evident. Pupillary dimensions and reaction normalized after rocuronium discontinuation of. The patient ultimately died due to refractory respiratory failure.

The third patient presented dilated (7 mm) non-reactive pupils after 126 h of continuous rocuronium infusion (creatinine 0.46 mg/dl, eGFR 132.1 ml/min/m^2). TCD imaging revealed normal cerebral blood flow. Pupils returned to normal after discontinuation and when sedation was withdrawn, the patient was able to fully communicate.

No patient received medications which could have resulted in pupillary dilation, although certain antimicrobials and other sedatives might have increased the effects of rocuronium by pharmacodynamic synergism. Interestingly, no papillary abnormality was seen when continuous infusion of cis-atracurium was used in our ICU (before shortage).

3. Discussion

COVID-19 ARDS patients may frequently require neuromuscular-blocking agent administration according to guidelines [1]. Cisatracurium is normally used, as its metabolism does not depend on hepatic or renal impairment, but a medication shortage during the pandemic forced the prescription of rocuronium [2]. Rocuronium is a steroidal nondepolarizing neuromuscular-blocking agent, acting by competitively antagonizing acetylcholine from binding to receptors on motor endplate, inhibiting depolarization [2].

Dilated, no-reactive pupils have not been reported as an adverse reaction of NMBA administration, as they are characterized by low lipophilicity, making them unable to surpass the Blood-Brain-Barrier (BBB). In animal models, when rocuronium is topically injected in the eye, mydriasis occurs [4]. However, the BBB may become impaired in Covid-19 patients, allowing access to the CNS [3].

To our knowledge, there are only two reports on the adverse effects of rocuronium on the CNS. Huaiwu et al., report pupil dilation in an ARDS patient under ECMO, after 79 h of rocuronium infusion, hypothesizing that inflammation and oxidative stress may possibly damage the BBB, increasing permeability to rocuronium [5]. Similar findings were also described in neonates, in which the BBB has not yet completely developed [6]. Schmidt et al., reported three patients, suffering from conditions known to disrupt the BBB, who presented reversible pupillary dilation with prolonged NMBA use, other than rocuronium [7].

Neurological symptoms from direct access of SARS-COV-2 to the brain, even severe encephalitis, have been reported [3]. Brain CT findings were unremarkable and transcranial doppler tracings did not suggest brain edema or hemorrhage in our patients. In addition, with sedation withdrawal, two of the patients regained consciousness (the third died within 5 days of intubation with refractory respiratory failure, so NMBA could not be withdrawn). Yet a degree of brain tissue inflammation impairing the BBB cannot be excluded; cerebrospinal fluid could not be obtained for analysis, as all the patients were under enhanced thromboprophylaxis treatment. We believe that under certain circumstances, rocuronium may cross the BBB and induce mydriasis. Noteworthy re-exposure to rocuronium in the first patient led to recurrence of pupillary dilation, although the patient had negative PCR for SARS-COV-2, indicating that BBB impairment might last for a long period.

Multiorgan involvement in Covid-19, in conjunction with increased NMBA concentrations due to prolonged administration and metabolization of rocuronium into active metabolites, may have resulted in the aforementioned neurological symptom. Continuous infusion, co-administration of drugs known to increase rocuronium's effects by pharmacodynamic synergism, such as amikacin, amphotericin-B, opioids or Mg sulphate and treatments that may impair hepatic function (such as Remdesivir), might all have contributed to increased rocuronium concentrations. Hence, we suggest that the combination of BBB disruption from SARS-COV-2 and high drug concentrations may have produced this alarming central effects. However, we cannot exclude the possibility of an unrecognized adverse reaction of continuous rocuronium administration, as limited data is available on extended rocuronium usage. Interestingly, we have not observed pupillary abnormalities in patients receiving cis-atracurium. Interestingly, pupillary dilation has never been reported in patients with other ARDS causes and cis-atracurium use. As increased concentrations are warranted for NMBA to cross the BBB, favorable cis-atracurium metabolism profile may have precluded its accumulation and thus CNS passage, although COVID-19 BBB impairment might still be present.

Fixed pupillary dilation in our cases was misleading; when mydriasis ensues in a patient, the presence of severe brain damage has to be excluded. Comprehensive neurological evaluation of Covid-19 patients when sedated and paralyzed, is indicated. Increased thromboembolic risk and enhanced anticoagulation used in many patients, renders them at increased risk of hemorrhagic complications, in addition to Covid-19 CNS involvement. Clinicians should keep these findings in mind.

4. Conclusion

Pupillary dilation must be considered when neuromuscular-blocking agents, especially rocuronium, are used for continuous infusion. Whether it could indicate CNS insult from the virus in COVID-19 ARDS patients, remains to be further evaluated.

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Declaration of competing interest

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