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Isolated reversible mydriasis was associated with the use of nebulized ipratropium bromide: a case series using quantitative pupilometer in Korea

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Background: Abnormal pupillary reactivity is a neurological emergency requiring prompt evaluation to identify its underlying causes. Although isolated unilateral mydriasis without accompanying neurological abnormalities is rare, it has occasionally been associated with nebulizer use. We aimed to quantitatively assess pupillary changes using a pupillometer in cases of isolated mydriasis, which has not been described in previous studies.

Methods: We retrospectively analyzed patients who developed unilateral mydriasis after using an ipratropium bromide nebulizer using a prospectively collected database in the intensive care unit (ICU) between April 2019 and August 2020. An automated pupillometer (NPi-100 or NPi-200) was used for quantitative pupillary assessment. The Neurological Pupil index (NPi) value at the time of unilateral mydriasis was assessed, and the latency before and after the application of the ipratropium bromide nebulizer was measured.

Results: Five patients with isolated mydriasis were identified (mean age, 68 years; male, 60.0%), none of whom had neurological abnormalities other than pupillary light reflex abnormalities. A quantitative pupillometer examination revealed that the affected pupil was larger (5.67 mm vs. 3.20 mm) and had lower NPi values (0.60 vs. 3.40) than the unaffected side. These abnormalities resolved spontaneously without treatment (pupil size, 3.40 mm; NPi, 3.90). The affected pupil had a prolonged latency of 0.38 seconds (vs. 0.28 seconds), which improved to 0.30 seconds with the resolution of the anisocoria.

Conclusions: In the ICU setting, it is important to keep in mind the ipratropium bromide nebulizer as the benign cause of unilateral mydriasis. Further, an automated pupilometer may be a useful tool for evaluating unilateral mydriasis.

Key Words: anisocoria; ipratropium bromide; mydriasis; nebulizer; pupillometer; uncal herniation

Original Article

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INTRODUCTION

A decrease in pupillary reactivity is considered a neurological emergency, as unresponsive and dilated pupils are frequently caused by compression or stretching of the oculomotor nerve during transtentorial or uncal herniation [1-3]. In general, this clinical condition is

commonly accompanied by other neurological abnormalities, such as deterioration of mental status, cranial nerve palsy, and motor weakness [4-6]. However, there have been some clinically significant cases in which isolated unilateral mydriasis occurs without any accompanying neurological deficits. Although rare, these instances are important to recognize, as they are generally benign, and are often associated with the use of specific pharmacologic agents, such as anticholinergic drug [7]. Here, we describe the characteristics of abnormal pupillary responses that occurred after the use of ipratropium bromide nebulizer in the intensive care unit (ICU) using a quantitative pupillometer.

KEY MESSAGES

- Ipratropium bromide nebulization should be recognized as a benign cause of unilateral mydriasis in the intensive care unit.
- Unilateral mydriasis caused by nebulized ipratropium bromide may resolve spontaneously without treatment.
- Automated pupillometers can provide an accurate, quantitative assessment of the pupil.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (No. H-2108-018-1241). The need for informed consent was waived by the board.

Study Population

We retrospectively enrolled 13 patients who were presented with unilateral mydriasis without other abnormal neurological examinations in the ICU between April 2019 and August 2020. Patients with a history of the following ophthalmologic conditions were excluded. Patients who diagnosed previous ocular diseases, such as (1) glaucoma (n=3), (2) diabetic retinopathy (n=1), (3) retinal disease (n=2), (4) optic nerve disease (n=1), or (5) severely diminished visual acuity (n=1), were excluded because these could affect pupillary light reflex (Figure 1).

Baseline Characteristics and Clinical Information

Clinical and demographic information, including age, sex, use of mechanical ventilation, primary diagnosis at ICU admission, concomitant use of medications, and brain imaging, were collected. Neurological severity was evaluated using the Glasgow Coma Scale every four hours during neurological monitoring.

Measurement of Quantitative Pupillary Reactivity

Quantitative pupillary light reflexes were assessed with an automated pupillometer (NPi-100 or NPi-200, NeurOptics Inc.) by neurointensivists or ICU nurses. When unilateral mydriasis was identified, pupillometer monitoring was conducted and repeated once mydriasis improved. The timing of pupillometer measurement varied for each individual patient, ranging from 3 hours to 24 hours after the development of mydriasis [8]. Using this device, pupil size (mm), latency (seconds), and Neurological Pupil index (NPi) were serially measured until pupillary abnormalities had resolved [9]. The values recorded at the onset of anisocoria were considered baseline values. The time of unilateral mydriasis and the time after the improvement of unilateral mydriasis were compared. NPi was automatically standardized on a 0–5 scale, with values below 3 indicating abnormal pupillary light reflex. [10].

Statistical Analysis

Data are presented as the mean±standard deviation, or as the median with interquartile range, depending on the data distribution. Categorical data were indicated by frequency and percentages. The Mann-Whitney U-test was used for continuous variables. Statistical analyses were performed using IBM SPSS version 23.0 (IBM Corp.), with a significant threshold set at a P-value of less than 0.05.

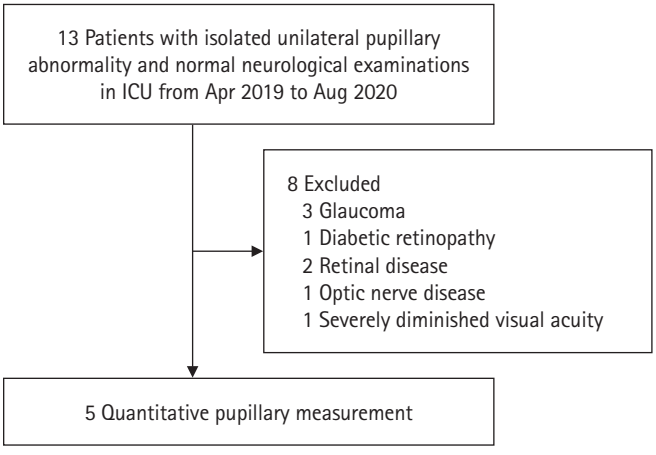

Figure 1. The flow of the study. ICU: intensive care unit.

RESULTS

Case 1

A 69-year-old man with chronic kidney disease, restrictive cardiomyopathy, and atrial fibrillation was admitted to the ICU for cardiopulmonary resuscitation due to respiratory failure. On admission, a baseline pupillary examination revealed normal, round, and reactive pupils symmetrical in size (3 mm, bilaterally). On day 3 in the ICU, the patient was extubated because the respiratory function was improved. Several hours later, the patient developed dilation of the left pupil, without any changes in mental status or other neurological signs. Examination with the pupillometer showed that the left pupil size measured 5.67 mm in diameter, with a decreased NPi value of 3.4 and prolonged latency of 0.31 seconds compared to the right pupil (with values of 3.42 mm, 4.0, and 0.25 seconds, respectively). Non-contrast brain computed tomography (CT) scan revealed no abnormal lesions affecting the pupillary light reflexes. A review of the patient's medications revealed that an ipratropium nebulizer (Atrovent UDV 500 μg/2 ml) had been administered just before anisocoria was noted. The anisocoria began to resolve within 6 hours. A follow-up pupillometer examination 12 hours following onset revealed normalization of the left pupil (size, 4.70 mm; NPi value, 4.4; latency, 0.28 seconds).

Case 2

An 87-year-old woman with a medical history of asthma, congestive heart failure, liver cirrhosis, and chronic kidney disease was admitted to the ICU for mechanical ventilation support due to asthma exacerbation. On day 5 in the ICU, mechanical ventilation was weaned off, and the patient complained of blurred vision 10 minutes after receiving ipratropium nebulizer therapy. A pupillary examination revealed that the right pupil was fixed (size, 4.87 mm; NPi value, 0; latency, 0.42 seconds) compared to the left pupil (1.95 mm, 4.6, and 0.34 seconds, respectively). All other neurological examinations were normal, except for right pupillary asymmetry. Non-contrast brain CT scan was unremarkable. The patient was treated with an ipratropium bromide nebulizer (Atrovent UDV 500 μg/2 ml) every 6 hours. A follow-up pupillometer evaluation after 24 hours after the onset of symptoms revealed normalization of the right pupil (size, 3.50 mm; NPi value, 4.4; latency, 0.28 seconds) to a size similar to the left (3.28 mm, 4.7 and 0.34 seconds, respectively).

Case 3

A 20-year-old man with a history of ventricular septal defect was admitted to the ICU with pneumonia associated with pulmonary edema. On physical examination, wheezing was noted in the bilateral lower lung fields, and the patient was subsequently treated with an ipratropium bromide nebulizer (Atrovent UDV 500 μg/2 ml). On ICU day 3, the right pupil was observed to be fixed and dilated, with no other focal neurological abnormalities (Figure 2). Subsequent pupillometer examination showed dilation of the right pupil (5.90 mm) with a decrease in NPi value of 0.6 and prolonged latency (0.38 seconds), compared to the left pupil (4.46 mm, 2.4, and 0.25 sec-

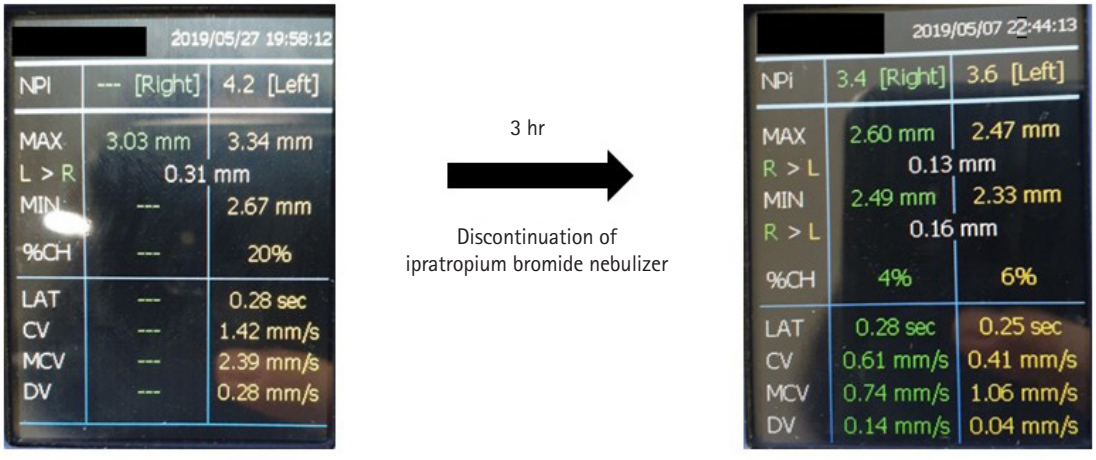

Figure 2. Change of pupillometer values. Pupillometer data showed an anisocoria (left) which improved after discontinuation of ipratropium bromide (right).

onds, respectively). Upon reviewing the patient's medications, it was found that the ipratropium bromide nebulizer had been administered immediately before anisocoria was identified. As there were no other neurological abnormalities, 1% pilocarpine eye drops were administered, and pupillary reflex did not change. At the follow-up examination 3 hours after discontinuing ipratropium bromide, the pupillometer test revealed recovery of the right pupil to baseline values of 3.44 mm (size), 2.1 (NPi), and 0.26 seconds (latency).

Case 4

An 81-year-old woman with pneumonia and septic shock was admitted to the ICU under mechanical ventilation. On ICU day 2, a manual assessment revealed that the right pupil was fixed and dilated (5 mm). All other neurological examination results were normal. An emergency brain CT scan revealed no abnormalities. A subsequent pupillometer examination confirmed that the right pupil was dilated and sluggish (size, 4.31 mm; NPi value, 2.4; latency, 0.37 seconds) compared to the left pupil (3.29 mm, 3.4, and 0.28 seconds, respectively). The patient had been receiving treatment with antibiotics for pneumonia, with ipratropium bromide nebulization (Atrovent UDV 500 μg/2 ml) every 8 hours. Indeed, the ipratropium bromide nebulizer was administered 35 minutes before the identification of anisocoria. Ipratropium was discontinued, and the anisocoria resolved spontaneously within 6 hours. A follow-up pupillometer examination revealed normalization of the right pupil (size, 2.21 mm; NPi value, 3.7; latency, 0.4 seconds), similar to the left (2.65 mm, 3.9, 0.33 seconds).

Case 5

A 57-year-old man with a history of lung cancer was admitted to the ICU for acute respiratory distress syndrome, where he was receiving ipratropium bromide nebulization (Atrovent UDV 500 μg/2 ml) every 6 hours. On day 4 in the ICU, the left pupil was dilated. A pupillometer evaluation revealed that the left pupil was fixed (size, 6.09 mm; NPi value, 0; latency, 0.43; undetectable percent change) compared to the right pupil (3.92 mm, 2.7, 0.34 seconds, and 18%, respectively). A medication review revealed that an ipratropium nebulizer had been administered just 25 minutes before anisocoria was identified, during which time the nurse had accidentally spilled and leaked ipratropium before inhalation. Because the patient showed no signs of neurological impairment, further testing, such as neuroimaging, was deemed necessary. Anisocoria resolved within 12 hours after discontinuation of ipratropium. A follow-up pupillometer examination confirmed that the left pupil had returned to normal (size, 2.86 mm; NPi value, 3.9; latency, 0.33 seconds), similar to the right (2.25 mm, 3.3, and 0.33 seconds, respectively).

Among the patients with anisocoria (male, 60.0%; median age, 68 years), none had any neurological abnormalities other than anisocoria. Four patients underwent brain imaging to exclude secondary mass lesions causing anisocoria (Table 1). Anisocoria developed a median of 17.5 minutes after the administration of the ipratropium bromide nebulizer. In addition, anisocoria resolved spontaneously within a median of 12 hours (median) after discontinuation of ipratropium bromide.

Quantitative pupillometer examination (Table 2, Supplementary Table 1) revealed that the affected pupils were larger (median, 5.67 mm vs. 3.20 mm; P=0.016) and showed lower NPi values (median, 0.60 vs. 3.40; P=0.045) compared to the pupil of the unaffected side. These abnormalities resolved spontaneously without treatment, with the affected pupil returning to a median size of 3.40 mm and a median NPi value of 3.90 (Table 2, Figure 3). Notably, the latency of the affected pupil was also prolonged (0.38 seconds vs. 0.28 seconds) but improved to 0.30 seconds as the anisocoria resolved.

DISCUSSION

This study found that the use of ipratropium bromide nebulizer was potentially associated with the occurrence of isolated unilateral anisocoria. All patients did not have any structural

Table 1. Baseline characteristics

Characteristics	Value
Sex (male:female)	3:2
Age (yr)	68 (43–78)
Use of mechanical ventilation	2 (40)
Diagnosis	
Septic shock	2 (40)
ARDS	2 (40)
Pulmonary edema	2 (40)
Cardiovascular diseases	2 (40)
CPR survivor	1 (20)
Dose of ipratropium bromide	
Atrovent UDV 500 μg/2 ml every 6 hr	3 (60)
Atrovent UDV 500 μg/2 ml every 8 hr	2 (40)
Imaging study	4 (80)

Values are presented as median (interquartile) or number (%).
ARDS: acute respiratory distress syndrome; CPR: cardiopulmonary resuscitation; UDV: unit dose vial.

Table 2. Pupillometer evaluation according to the use or absence of ipratropium bromide nebulizer

Value	After using of ipratropium bromide	After discontinuation of ipratropium bromide	P-value
Value of NPi on the ipsilateral side	0.60 (0.00–2.90)	3.90 (2.90–4.40)	0.045
Value of NPi on the contralateral side	3.40 (2.55–4.30)	4.20 (3.60–4.60)	0.401
Size of pupil on the ipsilateral side (mm)	5.67 (4.59–6.00)	3.40 (2.50–4.10)	0.016
Size of pupil on the contralateral side (mm)	3.20 (2.69–4.20)	2.82 (2.45–4.04)	0.602
Latency of pupil on the ipsilateral side (sec)	0.38 (0.34–0.43)	0.30 (0.27–0.37)	0.027
Latency of pupil on the contralateral side (sec)	0.28 (0.25–0.34)	0.33 (0.30–0.34)	0.454

Values are presented as median (interquartile range).
NPi: Neurological Pupil index.

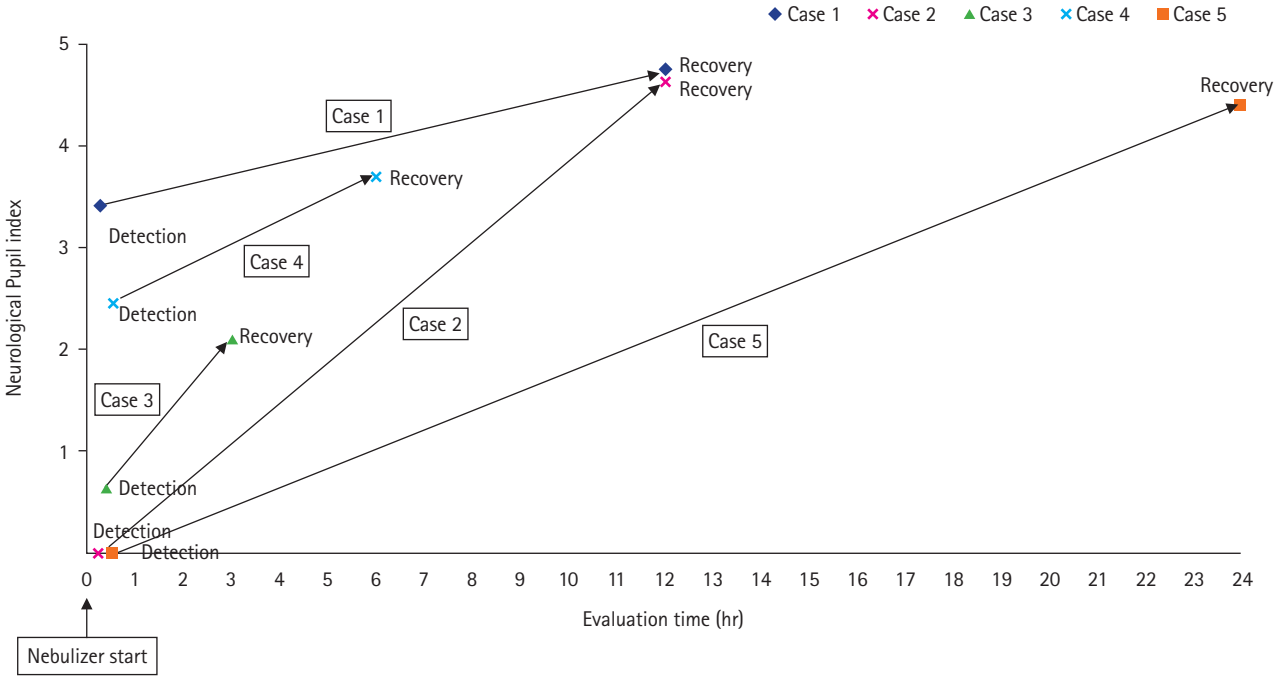

Figure 3. Neurological Pupil index value at the time of anisocoria detection and recovery.

intracranial abnormalities, and the anisocoria resolved spontaneously without additional treatment. When a patient presents with abnormalities in the pupillary light reflex, a thorough neurological examination is mandatory to rule out treatable causes of optic or oculomotor dysfunctions, including downward uncal herniation. If the neurological examination is unremarkable except for the light reflex, it is important to consider other causes of pupillary abnormality beyond structural issues. As demonstrated in this paper, anticholinergic drugs are one of the potential causes.

An accurate assessment of the underlying pathology of unilateral mydriasis is crucial. Although this condition is often benign, appropriate early evaluation and management are essential. Unilateral mydriasis can result from either structural or non- structural causes. If unilateral mydriasis is suspected to have a structural cause involving the oculomotor nerve, urgent evaluation and treatment are necessary to determine the clinical outcome [11]. However, it is crucial to be aware of other neurological signs and symptoms, such as altered level of consciousness or severe headache [12]. Without a structural cause, uneven pupils in critically ill patients may be attributed to nebulized anticholinergics, vasoactive agents, or seizures [13]. Nebulized ipratropium bromide, a frequently used pharmacological agent in the ICU, may cause this condition. Previous studies exploring the causes of pupillary abnormalities in the ICU patients showed that ipratropium bromide was the

culprit drug in 3% of cases [14]. In a retrospective chart review at our hospital, five cases of isolated anisocoria were identified among 1,009 patients who used ipratropium bromide nebulizers in the ICU during the study period. Therefore, we estimate that the incidence of unilateral mydriasis due to ipratropium bromide is approximately 0.5% in the ICU.

Ipratropium bromide is an anticholinergic agent that antagonizes cholinergic receptors and is commonly used as a bronchodilator and antisecretory agent in patients with respiratory complications. Direct exposure of an ipratropium nebulizer to a patient's eyes may result in unilateral or bilateral mydriasis, possibly due to improper positioning of the nebulizer mask. However, two patients (case 4 and 5) developed anisocoria while on mechanical ventilation. The exact cause is unknown, but we suspected a possibility of a malfunction in the in-circuit nebulizer system [15-19]. Its peak effects occur 30–60 minutes post-inhalation, with a duration of action lasting 3 to 6 hours [8]. Unilateral mydriasis is a known adverse effect of ipratropium bromide and typically resolves without further intervention. In cases where exposure to ipratropium bromide is not certain, a useful study may be to confirm pharmacologic mydriasis. As demonstrated in case 3, the use of 1% pilocarpine eye drops can help immediately differentiate whether anisocoria was due to pharmacological effects or underlying brain lesions [20]. Topical administration of 1% pilocarpine eye drops leads to miosis, in patients with a dilated pupil caused by third nerve compression, as the sphincter muscle remains intact. However, in cases of pharmacological mydriasis, the pupil size does not change even after administration of 1% pilocarpine, because the muscarinic cholinergic receptors are already blocked by ipratropium bromide as illustrated in case 3 [12].

In a clinical setting, pupil examination is frequently performed using a subjective manual light source, leading to variability and difficulties in interpreting the results [21]. Pupil measurements may differ between examiners, while detecting pupil reflexes can be particularly challenging in patients with small pupils, such as the elderly or those under sedation [22]. In contrast, an automated pupillometer provides an accurate and quantitative assessment of pupil size and reactivity, even in patients with small pupils or those under sedation. This tool is particularly valuable in evaluating episodic anisocoria [4,23,24].

Our study showed that while manual light tests may report a pupil as fixed, an automated pupillometer can reveal the pupil to be sluggish. Additionally, manual measurements of pupil size may be inaccurate; for example, manually detected mydriasis may show a different pupil size than measurements taken with a pupillometer. Consequently, automated pupillometry provides a more reliable and accurate assessment of unilateral mydriasis than manual light tests.

However, this study has several limitations. This is a single-center study with a limited number of patients. Therefore, our results need to be validated in a larger multicenter cohort. Further, it should be noted that a pupillometer may not accurately detect unilateral mydriasis in patients with pre-existing eye conditions, making it challenging to assess unilateral mydriasis. Given the nature of retrospective study design, the exact incidence of unilateral mydriasis due to ipratropium bromide nebulizer is unknown, warranting further studies. Moreover, we could not repeat the measurement of the pupillometer at regular intervals due to reimbursement issues at the time of the study period. Further studies are required to understand the dynamics of pupil recovery after stopping ipratropium bromide.

We would like to highlight that this study represents the first to use a pupilometer for the precise measurement of isolated mydriasis. The use of a pupillometer allows for a more accurate and objective assessment of pupillary changes, particularly isolated mydriasis, which has not been thoroughly quantified in previous studies. This methodology offers a novel approach to better understand the incidence and characteristics of mydriasis in clinical settings.

Although unilateral mydriasis is generally not a dangerous effect of ipratropium bromide, it can be mistakenly interpreted as a neurological emergency in patients in the ICU. This manifestation should therefore be considered in the differential diagnosis when it occurs in patients receiving ipratropium bromide, particularly if pupil size is the only abnormality, and no other focal neurological deficits are present. Unilateral mydriasis caused by ipratropium bromide nebulization may resolve spontaneously without treatment.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: SBK. Data curation: SHP, TJK. Formal analysis: SHP, TJK. Methodology: all authors. Project administration: SBK. Visualization: SHP, SBK. Writing – original draft: all authors. Writing – review & editing: SHP, SBK. All authors read and agreed to the published version of the manuscript.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4266/acc.2024.00983.

REFERENCES

1. Saju C, Barnes A, Kuramatsu JB, Marshall JL, Obinata H, Puccio AM, et al. Describing anisocoria in neurocritically ill patients. Am J Crit Care 2023;32:402-9.
2. Parmar KK, Dwaram S, Chacko B. Mydriasis in a critically ill patient. Anaesth Intensive Care 2009;37:861-2.
3. Lam BL, Thompson HS, Corbett JJ. The prevalence of simple anisocoria. Am J Ophthalmol 1987;104:69-73.
4. Kim TJ. Quantitative assessments of pupillary light reflexes in neurocritically ill patients. J Neurocrit Care 2022;15:79-87.
5. Kawasaki AK. Diagnostic approach to pupillary abnormalities. Continuum (Minneap Minn) 2014;20:1008-22.
6. Martínez-Ricarte F, Castro A, Poca MA, Sahuquillo J, Expósito L, Arribas M, et al. Infrared pupillometry: basic principles and their application in the non-invasive monitoring of neurocritical patients. Neurologia 2013;28:41-51.
7. Pennington KM, St Louis EK. "Don't believe your eyes" ipratropium induced mydriasis: a case report and review of the literature. Gen Med (Los Angel) 2016;4:255.
8. Montuschi P. Pharmacological treatment of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2006;1:409-23.
9. Larson MD, Behrends M. Portable infrared pupillometry: a review. Anesth Analg 2015;120:1242-53.
10. Kim TJ, Park SH, Jeong HB, Ha EJ, Cho WS, Kang HS, et al. Neurological pupil index as an indicator of neurological worsening in large hemispheric strokes. Neurocrit Care 2020;33:575-81.
11. Chang JY, Hong JH, Jeong JH, Nam SJ, Jang JH, Bang JS, et al. Therapeutic hypothermia after decompressive craniectomy in malignant cerebral infarction. Acute Crit Care 2014;29:93-8.
12. Kokulu K, Öner H, Özen C, Eroğlu SE, Altunok İ, Akça HŞ. Pharmacologic anisocoria due to nebulized ipratropium bromide: a diagnostic challenge. Am J Emerg Med 2019;37:1217.e3-4.
13. Afifi AK, Corbett JJ, Thompson HS, Wells KK. Seizure-induced miosis and ptosis: association with temporal lobe magnetic resonance imaging abnormalities. J Child Neurol 1990;5:142-6.
14. Portran P, Cour M, Hernu R, de la Salle S, Argaud L. Pupillary abnormalities in non-selected critically ill patients: an observational study. J Thorac Dis 2017;9:2528-33.
15. Iosson N. Images in clinical medicine: nebulizer-associated anisocoria. N Engl J Med 2006;354:e8.
16. Helprin GA, Clarke GM. Unilateral fixed dilated pupil associated with nebulised ipratropium bromide. Lancet 1986;2:1469.
17. Camkurt MA, Ay D, Akkucuk H, Ozcan H, Kunt MM. Pharmacologic unilateral mydriasis due to nebulized ipratropium bromide. Am J Emerg Med 2011;29:576.e5-6.
18. Pejic R, Klaric B. Transient anisocoria in a patient treated with nebulized ipratropium bromide. Am J Ophthalmol Case Rep 2017;7:11-3.
19. Krovvidi HP, Thillaivasan A. A benign cause for a unilateral dilated pupil in a critical care patient. Eur J Anaesthesiol 2008;25:692-3.
20. Bisquerra RA, Botz GH, Nates JL. Ipratropium-bromide-induced acute anisocoria in the intensive care setting due to ill-fitting face masks. Respir Care 2005;50:1662-4.
21. Zhao W, Stutzman S, DaiWai O, Saju C, Wilson M, Aiyagari V. Inter-device reliability of the NPi-100 pupillometer. J Clin Neurosci 2016;33:79-82.
22. Clark A, Clarke TN, Gregson B, Hooker PN, Chambers IR. Variability in pupil size estimation. Emerg Med J 2006;23:440-1.
23. Olson DM, Stutzman S, Saju C, Wilson M, Zhao W, Aiyagari V. Interrater reliability of pupillary assessments. Neurocrit Care 2016;24:251-7.
24. Kim TJ, Ko SB. Implication of neurological pupil index for monitoring of brain edema. Acute Crit Care 2018;33:57-60.