Disputes & Debates: Editors' Choice

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Editors' Note: Automated Quantitative Pupillometry in the Critically Ill: A Systematic Review of the Literature

In "Automated Quantitative Pupillometry in the Critically Ill: A Systematic Review of the Literature," Opic et al. summarized 58 articles (10 randomized trials) published from 1990 to 2019 on the use of automated pupillometry in adult critically ill patients. They reported that increased intracranial pressure (ICP), traumatic brain injury (TBI), ischemic brain damage, opioids and hypoxemia, and hypercarbia are potential confounders for pupillometry. Taccone et al. commented that increased ICP, TBI, and hypoxic ischemic brain injury (HIBI) should not be considered *confounders* of pupillometry (circumstances in which the test may be unreliable) but rather injuries that can *cause* pupillary abnormalities and that altered pupillary responses in these settings could be indicative of poor prognosis. In response, Opic et al. reinforced that medications can confound the pupillary assessment in certain circumstances but did not address the distinction between whether increased ICP, TBI, and HIBI typically *confound* or *cause* pupillary abnormalities. Larson commented that although opioids cause pupillary constriction, they do not affect the strength of the pupillary light reflex (PLR). They also pointed out that the systematic review did not include an article by Rollins et al., which described the persistence of a robust quantifiable PLR in the setting of opioid-induced hypoxia and hypercarbia. Opic et al. noted that they eliminated some articles based on the exclusion criteria of studies that used nonhandheld devices, but it is worth noting that Rollins et al. did, in fact, use a handheld device (the Neuroptics ForSite).[1,2] Opic et al. acknowledged that although the PLR involves both static and dynamic parameters, most of the studies they reviewed regarding the impact of opioids on pupillometry discussed their confounding impact on static parameters. Opic et al. and Larson reinforced that pupillometry always requires interpretation by a clinician based on an individual patient's circumstances.

Ariane Lewis, MD, and Steven Galetta, MD
Neurology® 2021;97:1138. doi:10.1212/WNL.0000000000012979

1. Rollins M, Feiner J, Lee J, Shah S, Larson M. Pupillary effects of high-dose opioid quantified with infrared pupillometry. *Anesthesiology*. 2014;121(5):1037-1044.
2. Du R, Meeker M, Bacchetti P, Larson M, Holland M, Manley G. Evaluation of the portable infrared pupillometer. *Neurosurgery*. 2005; 57(1):198-202.

Reader Response: Automated Quantitative Pupillometry in the Critically Ill: A Systematic Review of the Literature

Fabio S. Taccone (Brussels) and Giuseppe Citerio (Monza, Italy)
Neurology® 2021;97:1138–1139. doi:10.1212/WNL.0000000000012981

We read with interest the systematic review by Opic et al.,[1] which addressed the presence of potential confounders for outcome prediction in critically ill patients with automated pupillometry. Standard pupil variables such as size and constriction velocity were considered together

Author disclosures are available upon request (journal@neurology.org).

with the Neurologic Pupil Index (NPI), which is not influenced by medications or the environment.[2]

In addition, the clinical scenario after cardiac arrest is misleading. Extended hypoxic brain damage or increased intracranial pressure (ICP) would not be a confounder for pupillary assessment, even with the inclusion of the NPI criteria. These phenomena are the mechanisms inducing pupillary alterations in patients and the reason why clinicians monitor pupillary size and reactivity in this setting. Of course, sedatives or analgesics can influence pupillary metrics. However, NPI has been shown to be a predictive of poor outcomes in this setting, without false positives, within 24 hours after cardiac arrest.[3]

The same comment could be applied for traumatic brain injury (TBI). The presence of elevated ICP and brainstem compression may be the cause of pupillary dysfunction, rather than a confounder. Pupillary alterations are well-known predictors of poor outcomes after severe TBI and useful clinical monitoring tools in these patients.

1. Opic P, Rüegg S, Marsch S, Gut SS, Sutter R. Automated quantitative pupillometry in the critically ill: a systematic review of the literature. *Neurology*. 2021;97(6):e629-e642.
2. Shirozu K, Setoguchi H, Tokuda K, et al. The effects of anesthetic agents on pupillary function during general anesthesia using the automated infrared quantitative pupillometer. *J Clin Monit Comput*. 2017;31(2):291-296.
3. Oddo M, Sandroni C, Citerio G, et al. Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study. *Intensive Care Med*. 2018;44(12):2102-2111.

Author Response: Automated Quantitative Pupillometry in the Critically Ill: A Systematic Review of the Literature

Petra Opic (Basel, Switzerland) and Raoul Sutter (Basel, Switzerland)
Neurology® 2021;97:1139. doi:10.1212/WNL.0000000000012983

We thank the commenters for their valuable input on our study.[1] We consider it impossible to evaluate a patient for increased cranial pressure (ICP) using pupillometry without taking the patients' clinical context into account.[1] One of the items considered in clinical context is the use of medications that would alter pupillary reactions to exclude potentially false-negative or false-positive pupillometric results.

Patients with ICP often receive a wide range of concomitant medications. In this context, it is important to consider whether abnormal pupillary reactions reflect changes in intracranial pressure or are the result of concomitant medications (eg, ipratropium).[2,3] In other words, is there a factor present that causes a false-negative or false-positive pupillometric result?

The potential confounders listed in our review have all been shown to influence pupils to some degree and can be present at the same time during pupillary evaluation. When evaluating for one factor that could alter pupillary dynamics, concurrent influences from other potential confounding factors need to be excluded to avoid potential false-negative or false-positive results.

1. Opic P, Rüegg S, Marsch S, Gut SS, Sutter R. Automated quantitative pupillometry in the critically ill: a systematic review of the literature. *Neurology*. 2021;97(6):e629-e642.
2. Singhal NS, Josephson SA. A practical approach to neurologic evaluation in the intensive care unit. *J Crit Care*. 2014;29(4):627-633.
3. 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(6):1217.e3-1217.e4.
4. Chaudhry P, Friedman DI, Yu W. Unilateral pupillary mydriasis from nebulized ipratropium bromide: a false sign of brain herniation in the intensive care unit. *Indian J Crit Care Med*. 2014;18(3):176-177.

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Reader Response: Automated Quantitative Pupillometry in the Critically Ill: A Systematic Review of the Literature

Merlin D. Larson (San Francisco)
Neurology® 2021;97:1140. doi:10.1212/WNL.0000000000012982

Opic et al. are to be commended for listing the various factors that can affect the pupillary light reflex (PLR).[1] The PLR is like any other medical test because it requires interpretation by a physician who considers the result in the light of other information about the patient to determine a diagnosis and treatment. If the PLR has any value at all, then it seems preferable to get an objective measurement that can be time-stamped and trended over time.

I am concerned as to why the authors list opioids as a confounding factor. It is commonly known that opioids constrict the pupil, but the authors state that the article is focused on the PLR. Opioids do not alter the PLR, when measured by a parameter that is independent to the size of the pupil. Two important references that emphasize this point are missing in the article.[2,3] One relevant reference is included, but the point regarding the PRL is not commented on.[4] The Neurological Pupil Index (NPI) provides a measurement of the strength of the light reflex that is independent from pupil size and would not be altered by toxic doses of opioids.

1. Opic P, Rüegg S, Marsch S, Gut SS, Sutter R. Automated quantitative pupillometry in the critically Ill: a systematic review of the literature. *Neurology*. 2021;97(6):e629-e642.
2. Daniel M, Larson MD, Eger EI II, Noorani M, Weiskopf RB. Fentanyl, clonidine, and repeated increases in desflurane concentration, but not nitrous oxide or esmolol, block the transient mydriasis caused by rapid increases in desflurane concentration. *Anesth Analg*. 1995; 81(2):372-378.
3. Rollins MD, Feiner JR, Lee JM, Shah S, Larson M. Pupillary effects of high-dose opioid quantified with infrared pupillometry. *Anesthesiology*. 2014;121(5):1037-1044.
4. Larson MD, Kurz A, Sessler DI, Dechert M, Bjorksten AR, Tayefeh F. Alfentanil blocks reflex pupillary dilation in response to noxious stimulation but does not diminish the light reflex. *Anesthesiology*. 1997;87(4):849-855.

Author Response: Automated Quantitative Pupillometry in the Critically Ill: A Systematic Review of the Literature

Petra Opic (Basel, Switzerland) and Raoul Sutter (Basel, Switzerland)
Neurology® 2021;97:1140–1141. doi:10.1212/WNL.0000000000012984

We thank the reader for the interest in our study and the kind remarks.[1] Indeed, we consider the pupillary light reflex (PLR) a medical test that should be interpreted in light of a clinical context. Moreover, pupillometry has the advantage of being objective and allows for standardized assessment over time.

We were not able to include all suggested articles in the study because of our exclusion criteria concerning handhelds. Most of the studies involving opioids focused solely on static parameters. We showed a clear paucity of data regarding opioid dynamic pupillary parameters, and therefore, firm conclusions could not be drawn.

In addition, the article mentioned by the author investigated patients during hypoxemia and hypercarbia without mechanical ventilation.[2] The sympathetic drive caused by hypoxemia and hypercarbia can influence pupillary reactions and could potentially be counteracted by the mechanical ventilation ICU patients often receive. Moreover, a maximal miosis could be triggered with very high doses of opioids.[3,4] During maximal miosis with no possibility of further contraction, it remains unclear how any further pupillary contraction can be seen.

Author disclosures are available upon request (journal@neurology.org).

Finally, we recognize the term PLR tends to be ambiguous. In the context of our article, both static and dynamic parameters are considered in figure 4.

1. Opic P, Rüegg S, Marsch S, Gut SS, Sutter R. Automated quantitative pupillometry in the critically ill: a systematic review of the literature. *Neurology*. 2021;97(6):e629-e642.
2. Rollins MD, Feiner JR, Lee JM, Shah S, Larson M. Pupillary effects of high-dose opioid quantified with infrared pupillometry. *Anesthesiology*. 2014;121(5):1037-1044.
3. Parthvi R, Agrawal A, Khanijo S, Tsegaye A, Talwar A. Acute opiate overdose: an update on management strategies in emergency department and critical care unit. *Am J Ther*. 2019;26(3):e380-e387.
4. Fliegert F, Kurth B, Göhler K. The effects of tramadol on static and dynamic pupillometry in healthy subjects–the relationship between pharmacodynamics, pharmacokinetics and CYP2D6 metaboliser status. *Eur J Clin Pharmacol*. 2005;61(4):257-266.

CORRECTIONS

Geriatric Syndromes and Treatment Toxicities in Older Patients With Malignant Gliomas (4327)

Neurology® 2021;97:1141. doi:10.1212/WNL.0000000000013032

In the American Academy of Neurology annual meeting abstract "Geriatric Syndromes and Treatment Toxicities in Older Patients With Malignant Gliomas (4327)" by Alam et al.,[1] the first sentence of the Disclosure should read "Mr. Alam has nothing to disclose." The authors regret the error.

Reference

1. Alam A, Wasilewski A, Mohile N. Geriatric syndromes and treatment toxicities in older patients with malignant gliomas (4327). *Neurology*. 2020;94(15 suppl):4327.

Patient-Reported Symptom Severity in a Nationwide Myasthenia Gravis Cohort

Cross-sectional Analysis of the Swedish GEMG Study

Neurology® 2021;97:1141. doi:10.1212/WNL.0000000000013021

In the Research Article "Patient-Reported Symptom Severity in a Nationwide Myasthenia Gravis Cohort: Cross-sectional Analysis of the Swedish GEMG Study" by Petersson et al.,[1] the third sentence of the third paragraph of the Results should read: "Using a multivariate regression model, comparing patients with severe generalized disease to those without, we sought to identify factors correlating with higher MG-ADL score (Table 3)." The publisher regrets the error.

Reference

1. Petersson M, Feresiadou A, Jons D, et al. Patient-reported symptom severity in a nationwide myasthenia gravis cohort: cross-sectional analysis of the Swedish GEMG Study. *Neurology*. 2021;97(14):e1382-e1391.

Author disclosures are available upon request (journal@neurology.org).

Geriatric Syndromes and Treatment Toxicities in Older Patients With Malignant Gliomas (4327)

Neurology 2021;97;1141 Published Online before print October 29, 2021
DOI 10.1212/WNL.0000000000013032