Establishing Normative Data for Pupillometer Assessment in Neuroscience Intensive Care: The "END-PANIC" Registry

DaiWai M. Olson, Sonja E. Stutzman, Folefac Atem, Julia D. Kincaide, Thuy-Tien Ho, Byron A. Carlisle, Venkatesh Aiyagari

ABSTRACT

Background: Trained medical practitioners have been assessing the pupillary light reflex for more than 2 millennia. However, the interrater reliability of the pupillary light reflex remains low. To overcome the drawbacks of a subjective interpretation of pupillary size and reactivity, automated pupillometers are becoming increasingly commonplace, but practitioners do not have adequate data from which to judge whether the numerical values provided by the pupillometer are "within reference limits." **Methods:** This article details the methods used to create an extensive database of automated pupillometer readings and associated patient data (eg, intracranial pressure). **Discussion/Conclusions:** The "Establishing Normative Data for Pupillometer Assessments in Neuroscience Intensive Care" Registry will provide a large data set of pupillary size, reactivity, and speed of contraction in a cohort of patients admitted to a neuroscience intensive care unit with a variety of conditions. Analysis of this data set will help establish normative data for pupillometer readings for neurologically impaired patients. Exploratory analysis of this data set may also provide preliminary hypothesis generating data for future prospective studies on pupillary findings and trends in acute neurological conditions.

Keywords: assessment, pupillometer, study design, study methods

Questions or comments about this article may be directed to DaiWai M. Olson, PhD RN, at Daiwai.Olson@utsouthwestern.edu. He is an Associate Professor of Neurology and Neurotherapeutics, The University of Texas Southwestern Medical Center, Dallas, TX, and the Editor of the Journal of Neuroscience Nursing.

Sonja E. Stutzman, PhD, is Clinical Research Manager, The University of Texas Southwestern Medical Center, Dallas, TX.

Folefac Atem, PhD MS, is Assistant Professor of Biostatistics, The University of Texas Southwestern Medical Center, Dallas, TX.

Julia D. Kincaide, MPH, is Clinical Research Coordinator, The University of Texas Southwestern Medical Center, Dallas, TX.

Thuy-Tien Ho, PA, is Advanced Practice Provider, The University of Texas Southwestern Medical Center, Dallas, TX.

Byron A. Carlisle, RN BSN, is Nurse Manager, The University of Texas Southwestern Medical Center, Dallas, TX.

Venkatesh Aiyagari, MD, is Professor of Neurology and Neurotherapeutics, The University of Texas Southwestern Medical Center, Dallas, TX.

Disclosures: The study was funded by the UT Southwestern Medical Center Department of Nursing and by the NeurOptics company. Dr Olson is the Editor of JNN.

The authors declare no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jnnonline.com).

DOI: 10.1097/JNN.0000000000000296

Examination of eye function dates back more than 2,000 years. Galen, a Greek physician, is often credited as being the first physician to describe the pupillary light reflex (PLR).[1] Assessing the PLR is a low-tech high-volume task that is considered to be a standard part of the comprehensive neurological examination.[2,3] The traditional approach to assessing the PLR relies on trained observers using flashlights or penlights to determine the size, shape, and constriction velocity (CV) of the pupil. Recent evidence suggests that the traditional approach has limited interrater reliability.[4–6]

Modern technology and high-speed image processing have given rise to handheld pupillometry, and this technology is being quickly adapted into practice.[6,7] In contrast to the limited interrater reliability of human observers, pupillometers have been shown to have high interdevice reliability.[8] However, this is new technology, and there are currently insufficient data to describe the new normal for neurologically impaired patients. The normative data and central tendency measures associated with pupillometer assessments have not been fully established. The purpose of this methods article is to describe the methods for the development of the "Establishing Normative Data for Pupillometer Assessments in Neuroscience Intensive Care (END-PANIC)" Registry.

Background

A comprehensive assessment of cranial nerve (CN) function, including PLR, is an established element of the neurological examination.[2] The 12 CN pairs are located throughout the brain stem and diencephalon (except CN I).[9] Cranial nerves I and II emerge from the forebrain, whereas CNs III and IV emerge from the midbrain.[10,11] The second set of 4 (CNs V–VII) emerges from the pons. The final set of 4 (CNs IX–XII) emerges from the medulla.[9,11] For the purpose of this article, only the CNs that are involved in the PLR neural pathway (CNs II and III) will be discussed.

The pupil examination, including PLR, if conducted accurately, provides the assessor with information about the functional status of the optic (CN II) and oculomotor (CN III) nerves and the midbrain.[9] Cranial nerve II is the afferent tract of secondary sensory pathways that contains photosensitive ganglion cells forming the retinohypothalamic tract that perceive incoming light. Electrical signals carried along the efferent CN III cause the muscles of the eye to contract. These contractions result in movement of the eyeball but also in constriction of the pupil.[9] When the electrical signal in CN III is compromised, the pupil constriction will slow down or become nonreactive depending on the site and severity of the injury.

The sudden development of a slow or nonreactive pupil is often considered a true emergency. Although this sudden change is often detectable by the human eye (eg, blown pupil), the implications of more subtle changes are less well understood. Even a gradual increase in ipsilateral pupillary size, or the increase of pupil constriction latency (from brisk to sluggish reactivity), may signify the first indication of life-threatening transtentorial (uncal) herniation. Although the use of early detection of subtle pupillary changes using pupillometry is not known, urgent notification of the physician and relevant medical staff is warranted whenever a significant change in pupillary size or reactivity is noticed.[2]

Methods

This is a multicenter prospective registry of neurocritical care patients requiring pupillary assessments as part of their standard of care. The primary investigating institution is a large university hospital in the southwestern region of the United States. The primary site received approval by the institutional review board and is registered with ClinicalTrials.gov (NCT02804438). Patients are considered eligible for data collection if they are admitted to the critical care unit at a participating hospital and have a standard-of-care order for pupillary assessments.

Each of the participating sites already uses pupillometers as a standard of care.[12] Currently, the data

Data from the pupillometer is merged with data from the EMR.

collection sites include 4 neurocritical care units including 3 academic and 1 community hospitals in different states (California, Ohio, Texas, and Utah). There are no additional assessments or interventions performed in association with this registry. Data abstraction is performed on site, and the de-identified data are shared with the coordinating center and stored on a secure server maintained by the university.

The pupillometer used for this registry is the NPi-200 (Neuroptics, Inc). This device provides independent time-synched values for the left and right pupils. Individual patient pupil assessments are stored on the patient SmartGuard, which can save up to 168 readings. The readings from the SmartGuard can be viewed on the pupillometer or transferred to an electronic medical record (EMR) or electronic spreadsheet using the SmartGuard Reader by Omnikey. Table 1 provides a list of variables that can be obtained from the pupillometer SmartGuard.

Data collection involves 3 steps. In step 1, data from the pupillometer (Table 1) are obtained and downloaded into an electronic spreadsheet. Figure 1 provides a visual example of obtaining a pupillometer reading and transferring data from the SmartGuard to the EMR. In step 2, subject data are abstracted from the EMR to an electronic spreadsheet. Data abstracted from the EMR include demographic data, Glasgow Coma Scale score, the National Institutes of Health Stroke Scale score, the Hunt and Hess score, the Fisher score, the World Federation of Neurological Surgeons score, modified Rankin score on admission and at discharge, and medications known or hypothesized to influence pupil size or pupil reactivity (eg, barbituate, propofol, and narcotics). An example of the data collection form for 2 patients is provided as an example (Supplemental Digital Content 1, available at http://links.lww.com/JNN/A96). In step 3, data from steps 1 and 2 are uploaded into SAS v9.4 (for Windows) and merged into a single data set.

Discussion

The study protocol has been successfully used to acquire and store source data and to produce a multicenter composite data set. The registry is currently active with data entry from more than 800 patient records with more than 20 000 pupillometer readings. Initial data analysis has shown that common variables are compatible with the data analysis plan. The registry faced an initial challenge in designing

TABLE 1. Variables Obtained From Pupillometer SmartGuard

Variable	Definition	Units
Patient	The patient identification number	-
Date	The date and time of the observation	mo/d/y; h:min
NPi[a]	Neurological pupil index. A derived value that compares the reading obtained against normative models.	Scaled value between 0 and 5
Size[a]	Initial size. The size of the pupil before light stimulation	mm
Min[a]	Minimum size. The smallest recorded pupil size	mm
%[a]	The percent change in pupil size	%
CV[a]	Constriction velocity. The change in size divided by the time during which constriction occurs in response to light.	mm/s
MCV[a]	Maximum constriction velocity. The peak velocity noted during constriction.	mm/s
DV[a]	Dilation velocity. The change in size (after light stimulus has ended) as the pupil dilates, divided by time.	mm/s
Lat[a]	Latency. The period from initial light stimulus to the start of pupillary constriction.	s

[a]Values will appear for the left and right pupils (eg, NPiL, NPiR, sizeL, sizeR, etc).

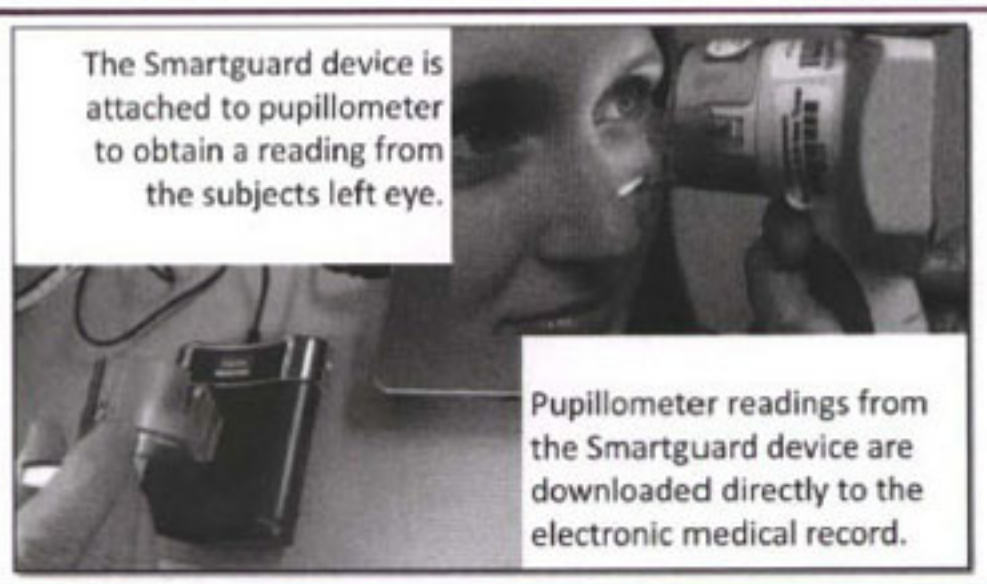
a data collection form that could be completed in a reasonably short period (ie, by a nurse) yet provide enough detail for future analyses. As shown in Table 1, the study currently includes only those variables deemed most commonly associated with PLR assessments. As additional data are collected and additional sites are added, variables may be revised.

The pupillometer measures pupil size, pupil latency, CV, and dilation velocity. These variables are from the algorithm for the neurological pupil index (NPi). The NPi enables clinicians to quickly assess all of the previously mentioned variables in 1 number. The NPi ranges from 0 to 5, with a score of 3 or higher indicating normal pupillary responses. A score of 3 or less specifies an abnormal pupil response and the potential need for further assessment or intervention. A score of 0 indicates that no constriction is detected. The pupillometer has been shown to have excellent agreement among devices, showing very high reliability, which addresses some shortcomings of human error, as previously described in the literature.[8]

Human error is a factor when conducting behavioral interventions, and traditional pupil examinations are no exception. Determining the size, shape, and reactivity of pupils can be difficult due to eye color, patient compliance, and ambient lighting. Olson et al[4] found that human pupil assessments were in agreement only approximately 79% of the time; moreover, when the pupil's reactivity is questionable or compromised, there is only 49% agreement between 2 clinician raters. If a pupil is inaccurately deemed fixed, unnecessary medical interventions may occur, potentially placing the patient at a higher risk for complications. Consistent pupil readings with trend data would allow the team to intervene early and potentially avoid unnecessary interventions.

In a comatose or heavily sedated patient, the PLR represents one of the few elements of the neurological

FIGURE 1 Obtaining a Pupillometer Reading and Downloading the Results



examination that can repeatedly be obtained. In certain situations, it may be undesirable to turn off continuous sedation, and the "pupil check" might be the only component of the neurological examination completed.[13] For instance, patients given a diagnosis of high-grade subarachnoid hemorrhage and obstructive hydrocephalus (high risk for elevated intracranial pressure and central brain herniation) may require heavy sedation without interruption.[14]

Limitations

The registry will have several limitations, and most of these are common to any and all registry data. First, the data are voluntarily entered by hospitals that choose to participate. Therefore, there is the potential of a selection bias. Second, the time stamp for the pupillometer is used to link the time stamp from data abstracted from the EMR, and the sampling period for the EMR is typically once per hour (sometimes less frequently). This might create a problem in the following fictitious example: a patient has a neurological change at 1:30 PM, and the nurse performs a pupillometer examination at 1:57 PM and then afterward performs a comprehensive neurological examination. The neurological change may erroneously be documented as having occurring "after" the pupillometer examination. It should be noted that the results from manual pupil examinations are not collected; this may affect the ability to translate findings from this registry to institutions that do not use pupillometers.

Conclusions

This article describes the methods to develop a large registry of pupillometer data and associated patient variables. The data will be important for defining the normative values and central tendencies of key measures of NPi and CV. Moreover, the data can be used to address key questions regarding pupillary findings among subsets of patient populations commonly cared for by neuroscience nurses.

Acknowledgments

The authors thank research interns, Karla Alvarado, Soo Min Pak, and Christine Yu who assisted with data collection.

References

1. Thompson HS, Corbett JJ. Asymmetry of pupillomotor input. *Eye (Lond)*. 1991;*5*(pt 1):36–39.
2. Bader MK, Littlejohns LR, Olson DM. *AANN Core Curriculum for Neuroscience Nursing*. 6th ed. Glenview, IL: American Association of Neuroscience Nurses; 2016.
3. Greenberg MS. *Handbook of Neurosurgery*. 8th Ed. New York, NY: Thieme; 2016.
4. Olson DM, Stutzman S, Saju C, Wilson M, Zhao W, Aiyagari V. Interrater reliability of pupillary assessments. *Neurocrit Care*. 2016;*24*(2):251–257.
5. Omburo L, Stutzman S, Supnet C, Choate M, Olson DM. High variance in pupillary exam findings among post-anesthesia care unit nurses. *J Post Anesth Nurs*. 2016;*32*(3):219–224.
6. Couret D, Boumaza D, Grisotto C, et al. Reliability of standard pupillometry practice in neurocritical care: an observational, double-blinded study. *Crit Care*. 2016;*20*:99.
7. Zafar SF, Suarez JI. Automated pupillometer for monitoring the critically ill patient: a critical appraisal. *J Crit Care*. 2014; *29*(4):599–603.
8. 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.
9. Wilson-Pauwels L. *Cranial Nerves: Function and Dysfunction*. 3rd ed. Shelton, CT: People's Medical Pub House; 2010.
10. Bader MK, Littlejohns LR, American Association of Neuroscience Nurses. *AANN Core Curriculum for Neuroscience Nursing*. 5th ed. Glenview, IL: American Association of Neurosciene Nurses; 2010.
11. Blumenfeld H. *Neuroanatomy Through Clinical Cases*. Sunderland, MA: Sinauer; 2002.
12. Olson DM, Bazil J. Pupillometer. In: Wiegand DJL-M, American Association of Critical-Care Nurses, eds. *AACN Procedure Manual for Critical Care*. 7th ed. St Louis, MO: Elsevier/Saunders; 2016.
13. Olson DM, Graffagnino C. Consciousness, coma, and caring for the brain-injured patient. *AACN Clin Issues*. 2005;*16*(4):441–455.
14. Stevens RD, Huff JS, Duckworth J, Papangelou A, Weingart SD, Smith WS. Emergency neurological life support: intracranial hypertension and herniation. *Neurocrit Care*. 2012;*17*(suppl 1):S60–S65.