Pupillary Light Reflex Variability as a Predictor of Clinical Outcomes in Subarachnoid Hemorrhage

CE 1.5 ANCC Contact Hours

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ABSTRACT

BACKGROUND: A change in the pupillary light reflex (PLR) is a sensitive indicator for detecting expanding intracranial lesions. Changes in PLR may be a prognostic marker for patients with intracranial lesions. The purpose of this analysis was to explore how PLR readings, size, constriction velocity (CV), dilation velocity (DV), Neurologic Pupil Index (NPi), and latency predict clinical outcome in patients with subarachnoid hemorrhage. **METHODS:** This is a secondary analysis of prospectively collected multicenter registry data. The within-subject standard deviation (W_{SD}) of PLR values, NPi, size, CV, DV, and latency were explored as predictors of discharge modified Rankin Scale (mRS) in patients with subarachnoid hemorrhagic. **RESULTS:** Among 4403 pupillary readings from 82 patients with a diagnosis of subarachnoid hemorrhage, with a mean age of 57.7 years, the admission Glasgow Coma Scale median score was 14 (eye, 4; verbal, 4; motor, 6), and the mRS median was 0 on admission and 4 at discharge. Correlation between standard deviation of PLR values and discharge mRS was moderate and negative ($r = -0.3$ to -0.47, $P < .01$). The standard deviations for NPi, size, CV, and DV were significant for predicting discharge mRS ($r^2 = 0.23$–0.28, $P < .05$) after controlling for admission Glasgow Coma Scale. **CONCLUSION:** Patients with higher W_{SD} PLR values showed better outcomes (ie, lower mRS at discharge), suggesting that patients with narrower W_{SD} PLR are at a higher risk for poor outcomes.

Keywords: modified Rankin Scale, neuroscience nursing, pupillary light reflex, standard deviation, subarachnoid hemorrhage

Bedside nursing assessment of the pupil is a key component of the neurological examination in neurocritical care patients.[1] The pupillary examination has traditionally been used to monitor these patients; this examination includes assessment of pupil size, shape, symmetry, and reactivity to light.[1–3] The pupillary light reflex (PLR), or reactivity to light, portion of the pupillary assessment has potential for early detection of expanding or emerging intracranial lesions.[4] Current practice includes mostly subjective estimation of pupil size in millimeters, and it is common to hear descriptive terms such as "small," "moderate," or "large" accompanied by terms such as "brisk," "sluggish," or "fixed" to determine the reactivity of the pupil.[1,5] Today, an objective way to perform pupillary examination is by using the automated pupillometer to obtain more reliable results[6,7] and provide several new variables that are not available with subjective assessment (eg, constriction and dilation velocities).[8]

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Recent studies have shown some association between pupillometer readings and intracranial pressure (ICP),[2] neurological deterioration,[9] pain,[10,11] sedative response,[12] and as a predictor of poor clinical outcomes.[13] Many of these studies have been conducted with modern pupil technology, which allows the clinician to obtain objective or numerical values that are associated with the pupillary examination. The pupillometer used for this registry was the NPi-200 (NeurOptics, Inc). This device is the only handheld optical scanner available in the U.S.A. that objectively measures pupil size, and pupil reactivity in patients requiring neurological pupil examinations.[8] There are no studies that explore associations between the pupillometer values and patient outcomes for patients with subarachnoid hemorrhage (SAH).[14–16] This study will explore how PLR readings (size, CV, DV, NPi, and LAT) might predict clinical outcomes in patients with SAH. We hypothesize that the variation of pupillometer values is associated with modified Rankin Scale (mRS) at discharge.

Methods

This is a secondary analysis of a prospective multicenter END-PANIC registry.[17] The pupillometer used for this registry was the NPi-200 (NeurOptics, Inc). This device is the only handheld optical scanner available in the U.S.A. that objectively measures pupil size and pupil reactivity in patients requiring neurological pupil examinations. These variables include maximal and minimal diameter, latency (LAT), constriction velocity (CV), dilation velocity (DV), and the Neurologic Pupil Index (NPi) (a proprietary algorithm unique to NeurOptics which computes an overall score of pupil reaction to light). The NPi is a unique new variable.[8] Data were collected from 3 neurocritical intensive care units (NICUs) in the United States that use pupillometers as standard of care. Patients are included in the registry if they are older than 18 years and were admitted to the NICU with SAH (including aneurysmal SAH [aSAH]). The END-PANIC registry received approval by the institutional review board and is registered with ClinicalTrials.gov (NCT02804438).

The patient baseline data included age, sex, race, primary diagnosis (SAH and aSAH), severity (Hunt & Hess score), and admission Glasgow Coma Scale (GCS) and mRS. Clinical variables included pupillometer readings obtained during the NICU stay. The NICU and hospital length of stay (LOS), and mRS at discharge were recorded. Descriptive statistics included measures of central tendency (means, standard deviations, medians, and ranges) for continuous variables and frequencies and percentages for categorical variables.

Higher variation in pupillometer readings is associated with lower discharge mRS scores.

The within-subject standard deviation (W_{SD}) values of PLR readings (size, CV, DV, NPi, and LAT) were first derived to provide an estimate of the spread of data for each individual patient. The W_{SD} values were then used as predictors of the mRS at discharge. Correlation and logistic regression analysis for normally distributed data was performed using SAS v9.4.

Results

Eighty-two patients were included in the data analysis, with a total of 4403 pupillary readings (range of readings, 2–384 per patient). Patient mean age was 57.7 years; 66% were female (n = 54); primary diagnosis was 77% SAH (n = 63) and 23% aSAH (n = 19); and Hunt & Hess scale showed 40% grade 1 (n = 33), 27% grade 2 (n = 22), and 33% grade 3 (n = *27*), with no cases in Hunt & Hess grades 4 and 5. The admission GCS median score was 14 (eye, 4; verbal, 4; motor, 6). On admission, mRS distribution was as follows: 78.1% score 0 (n = 64), 8.5% score 1 (n = 7), 1.2% score 2 (n = 1), 4.9% score 3 (n = 4), 2.4% score 4 (n = 2), and 4.9% score 5 (n = 4). The discharge mRS distribution was as follows: 22% score 0 (n = 18), 13.4% score 1 (n = 11), 7.3% score 2 (n = 6), 6% score 3 (n = 5), 26.9% score 4 (n = 22), 13.4% score 5 (n = 11), and 11% score 6 (n = 9). The mean NICU LOS was 14.2 days with a range of 0 to 40 days, and that for hospital LOS was 17.7 days with a range of 0 to 56 days (Table 1). A Wilcoxon test indicates a statistical significance difference among the mRS on admission and at discharge (Sign test = 28, $P < .0001$).

To explore within-subject variation, the standard deviation for PLR values was computed for each patient. Bivariate analysis showed a moderate negative correlation with the dependent variable, mRS at discharge, and the W_{SD} for PLR values in both eyes ($r = -0.3$ to -0.47, $P < .01$; Table 2). A logistic regression after controlling for admission GCS indicated that W_{SD} for NPi, size, CV, and DV for both eyes are predictors of mRS at discharge ($\beta = -1.21$ to -10.21, $P < .05$), suggesting that higher variation in pupillometer readings is associated with lower scores in mRS at discharge suggesting that higher variation in pupillometer readings is associated with lower scores in mRS at discharge

TABLE 1. Baseline Characteristics of Demographic and Standard Deviation of Pupillometer Readings

Variable	N	Mean (SD)	Median	Range
Age, y	82	57.7 (15.8)	54	19–87
GCS	82	11.4 (4.1)	14	3–15
GCSeye	82	3.3 (1.9)	4	1–5
GCSverbal	82	3.0 (1.2)	4	1–5
GCSmotor	82	5.1 (1.5)	6	1–6
mRS on admission	82	0.6 (1.3)	0	0–5
mRS at discharge	82	2.8 (2.1)	4	0–6
NICU length of stay	82	14.2 (9.0)	14	0–40
Hospital length of stay	82	17.7 (11.9)	16	0–56

Abbreviations: GCS, Glasgow Coma Scale; mRS, modified Rankin Scale; NICU, neurocritical intensive care unit.

(Supplemental Table 3, Supplemental Digital Content 1, available at http://links.lww.com/JNN/A167).

Discussion

Assessing the PLR provides vital information on intracranial dynamics.[5,18] Findings from this study support the statement that the variation of pupillometer values may predict outcome measures at discharge. This suggests that patients whose visual pathways have more adaptation to change and response to treatment, showed in this study as higher W_{SD} PLR values, will be more likely to have better clinical outcomes (low scores in mRS at discharge) as evidenced by the negative correlation between W_{SD} PLR values and mRS at discharge.

The association between PLR and mRS may reflect dynamic changes in ICP unresponsive to therapy. As ICP increases, there is an increased risk for central brain herniation. The mechanical forces and brain compression potentially prevent transmission of electrical impulses along the oculomotor cranial nerve, resulting in delayed or absent constriction of the pupil.[19] Although loss of PLR (fixed pupil) can and does occur without accompanying central herniation,[20] a growing body of research has found associations between PLR assessed by automated pupillometry and changes in ICP.[4] McNett et al[2] published findings that show a

TABLE 2. Correlation for W_{SD} PLR Values and mRS at Discharge

		mRS at Discharge	
Variables	Range	Correlation Coefficient	*P*
W_{SD} NPi RE	0–1.73	−0.36934	.0006
W_{SD} NPi LE	0–1.80	−0.36593	.0007
W_{SD} MIN RE	0–1.03	−0.40264	.0002
W_{SD} MIN LE	0–1.04	−0.34272	.0016
W_{SD} MAX RE	0–1.13	−0.31327	.0042
W_{SD} MAX LE	0–1.25	−0.30071	.0061
W_{SD} CV RE	0–0.97	−0.40565	.0002
W_{SD} CV LE	0–0.90	−0.41447	.0001
W_{SD} DV RE	0–0.32	−0.46787	< .0001
W_{SD} DV LE	0–0.42	−0.38578	.0003
W_{SD} LAT RE	0–0.96	−0.33544	.0021
W_{SD} LAT LE	0–0.32	−0.29704	.0067

Abbreviations: CV, constriction velocity; DV, dilation velocity; LAT, latency; LE, left eye; MAX, maximum size; MIN, minimum size; mRS, modified Rankin Scale; NPi, Neurologic Pupil Index; PLR, pupillary light reflex; RE, right eye; W_{SD}, within-subject standard deviation.

statistically significant relationship between NPi less than 3 and increased ICPs. Zafar and Suarez[21] suggest that PLR values are important in determining neurologic outcomes and prognosis for NICU patients, and Aoun et al[22] suggest that NPi changes are strongly associated with the advent of delayed cerebral ischemia. The clinical relevance of these results strengthens the contention that PLR values could be an early herald of clinical changes.

The principal limitation of this study is that, despite the GCS being controlled for in the regression model, there may be other potential confounders that should be analyzed in future studies (eg, the Hunt & Hess score, nonreactive pupils that will have lower standard deviation and discriminate between diagnoses SAH/aSAH), and this might have influenced these results. Another recognized limitation is temporal variance. Nursing staff were tasked to perform serial PLR assessments, but the interval between assessments and the number of assessments per subject varied. Automated pupillometry is becoming more routine, and various devices are being marketed and found reliable.[7,23] As the evolution in technology progresses, additional and more frequent data may reveal specific trends and relationships in PLR findings that alter the conclusions reached from this analysis.

Conclusion

Patients with higher W_{SD} in PLR values had lower (better) discharge mRS, suggesting that patients unable to respond to changes in intracranial dynamics are at a higher risk for poor outcomes. Pupillary light reflex values may be a marker for neurocritical care patients' outcomes.

References

1. Papangelou A, Zink EK, Chang WW, et al. Automated pupillometry and detection of clinical transtentorial brain herniation: a case series. *Mil Med*. 2018;183(1–2):e113–e121.
2. McNett M, Moran C, Janki C, Gianakis A. Correlations between hourly pupillometer readings and intracranial pressure values. *J Neurosci Nurs*. 2017;49(4):229–234.
3. Anderson M, Elmer J, Shutter L, Puccio A, Alexander S. Inte grating quantitative pupillometry into regular care in a neurotrauma intensive care unit. *J Neurosci Nurs*. 2018;50(1):30–36.
4. Chen JW, Gombart ZJ, Rogers S, Gardiner SK, Cecil S, Bullock RM. Pupillary reactivity as an early indicator of increased intracranial pressure: the introduction of the Neurological Pupil index. *Surg Neurol Int*. 2011;2:82.
5. Shoyombo I, Aiyagari V, Stutzman SE, et al. Understanding the relationship between the Neurologic Pupil index and constriction velocity values. *Sci Rep*. 2018;8(1):6992.
6. Meeker M, Du R, Bacchetti P, et al. Pupil examination: validity and clinical utility of an automated pupillometer. *J Neurosci Nurs*. 2005;37(1):34–40.
7. 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.
8. Olson DM, Fishel M. The use of automated pupillometry in critical care. *Crit Care Nurs Clin North Am*. 2016;28(1):101–107.
9. Taylor WR, Chen JW, Meltzer H, et al. Quantitative pupillometry, a new technology: normative data and preliminary observations in patients with acute head injury. Technical note. *J Neurosurg*. 2003;98(1):205–213.
10. Hofle M, Kenntner-Mabiala R, Pauli P, Alpers GW. You can see pain in the eye: pupillometry as an index of pain intensity under different luminance conditions. *Int J Psychophysiol*. 2008;70(3):171–175.
11. Paulus J, Roquilly A, Beloeil H, Théraud J, Asehnoune K, Lejus C. Pupillary reflex measurement predicts insufficient analgesia before endotracheal suctioning in critically ill patients. *Crit Care*. 2013;17(4):R161.
12. Haddock JH, Mercante DE, Paccione R, et al. Use of digital pupillometry to measure sedative response to propofol. *Ochsner J*. 2017;17(3):250–253.
13. Hoffmann M, Lefering R, Rueger JM, et al. Pupil evaluation in addition to Glasgow Coma Scale components in prediction of traumatic brain injury and mortality. *Br J Surg*. 2012;99(suppl 1):122–130.
14. Rankin J. Cerebral vascular accidents in patients over age of 60. *Scott Med J*. 1957;2:200–215.
15. Bonita R, Beaglehole R. Recovery of motor function after stroke. *Stroke*. 1988;19(12):1497–1500.
16. Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19(5):604–607.
17. Olson DM, Stutzman SE, Atem F, et al. Establishing normative data for pupillometer assessment in neuroscience intensive care: the "END-PANIC" registry. *J Neurosci Nurs*. 2017;49(4):251–254.
18. Emelifeonwu JA, Reid K, Rhodes JK, Myles L. Saved by the pupillometer!—a role for pupillometry in the acute assessment of patients with traumatic brain injuries? *Brain Inj*. 2018;32(5):675–677.
19. Greenberg MS. *Handbook of Neurosurgery*. 8th ed. New York, NY: Thieme Medical Publishers; 2016.
20. Chung DY, Edlow BL. Teaching NeuroImages: traumatic blown pupil without herniation. *Neurology*. 2017;88(19):e190–e191.
21. Zafar SF, Suarez JI. Automated pupillometer for monitoring the critically ill patient: a critical appraisal. *J Crit Care*. 2014;29(4):599–603.
22. Aoun SG, Stutzman SE, Vo PN, et al. Detection of delayed cerebral ischemia using objective pupillometry in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2019;1–6.
23. Salah-Mabed I, Saad A, Gatinel D. Assessing repeatability of pupillometric measurements in the eyes of refractive surgery candidates using infrared pupillometer. *J Refract Surg*. 2017;33(8):552–557.

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