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Pupillary light reflex measured with quantitative pupillometry has low sensitivity and high specificity for predicting neuroworsening after traumatic brain injury

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ABSTRACT

Background: Triage and neurological assessment of the 1.7 million traumatic brain injuries occurring annually is often done by nurse practitioners and physician assistants in the emergency department. Subjective assessments, such as the neurological examination that includes evaluation of the pupillary light reflex (PLR), can contain bias. Quantitative pupillometry (QP) standardizes and objectifies the PLR examination. Additional data are needed to determine whether QP can predict neurological changes in a traumatic brain injury (TBI) patient.

Purpose: This study examines the effectiveness of QP in predicting neurological decline within 24 hours of admission following acute TBI.

Methodology: This prospective, observational, clinical trial used pragmatic sampling to assess PLR in TBI patients using QP within 24 hours of ED admission. Chi-square analysis was used to determine change in patient status, through Glasgow Coma Scale (GCS), at baseline and within 24 hours of admission, to the QP.

Results: There were 95 participants included in the analysis; of whom 35 experienced neuroworsening, defined by change in GCS of >2 within the first 24 hours of admission. There was a significant association between an abnormal Neurological Pupil index (NPi), defined as NPi of <3, and neuroworsening ($p < .0001$). The sensitivity (51.43%) and specificity (91.67%) of abnormal NPi in predicting neuroworsening were varied.

Conclusion: There is a strong association between abnormal NPi and neuroworsening in the sample of TBI patients with high specificity and moderate sensitivity.

Implications: NPi may be an early indicator of neurological changes within 24 hours of ED admission in patients with TBI.

Keywords: Acute care; assessment; emergency medicine; nurse practitioners; traumatic brain injury.

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Introduction

Nurse practitioners (NPs) and physician assistants (PAs) are increasingly being called upon to evaluate patients with traumatic brain injury (TBI) in the emergency department (ED) and prehospital setting (Geller & Swan, 2021; Lee et al., 2020). Worldwide, TBI is a major concern in both the health care sector and general population (Fehily & Fitzgerald, 2017). From ground-level falls to head trauma occurring during sporting activities, the incidence and public awareness of TBI are increasing (Dewan et al., 2019). Multiple neurosurgical interventions exist to manage TBI, and early recognition and intervention are expected to improve patient outcomes (Tenovuo et al., 2021). When a TBI warrants an ED visit, nurses, NPs, or PAs are routinely the first to assess a patient, and a routine neurological assessment can be vital in unearthing abnormalities not otherwise noted (El Ahmadieh et al., 2021). A part of the neurological examination is assessing pupillary light reflex (PLR); given the limited reliability of PLR assessment by humans, quantitative pupillometry (QP) is being adopted at institutions across the globe (Giamarino & Reynolds, 2022; Olson et al., 2016). Using QP to assess PLR might indicate a forthcoming patient examination

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change or neurological decline to the clinical team (Lussier, Olson, et al., 2019). What is not known is how QP may affect our ability to predict a neurological status change after TBI in the acute phase of treatment. Therefore, this study aims to examine whether QP could help predict a neurological decline in the first 24 hours for a patient with TBI.

Background

Worldwide, TBI is a leading cause of disability in people younger than 40 years (Dang et al., 2017). The Centers for Disease Control and Prevention estimates that approximately 1.7 million TBIs occur annually in the United States alone. Of these, approximately 275,000 require hospitalization and 52,000 die as a result (Chen et al., 2014). Recent analysis has revealed that TBIs have been linked to progressive neurological degeneration, although it is difficult to diagnose (Graham & Sharp, 2019). With such a large range of effects, there must be a more accurate way to identify patients who require treatment.

The act of injury occurring from the TBI is believed to be related to the coup–contrecoup action that results in further neural damage by route of edema or hemorrhage (Pelieu et al., 2019). The effects on each patient vary from sensory, motor, perceptual, cognitive processing, attention-based, physiological, and/or behavioral in nature (Ciuffreda et al., 2017). Accurate acute assessment of the severity of TBI is crucial to treatment and patient outcomes. This begins with the neurological examination, which includes an evaluation of the PLR. The pupillometer is an automated device that allows for a standardized PLR assessment with a more accurate and reliable reading than a pen light (Olson et al., 2016). In contrast to a penlight, the pupillometer is a more accurate tool for determining pupil reactivity and size during neurological assessments (Olson & Fishel, 2016). In addition, the pupillometer could also identify early neurological function changes (Lussier, Olson, et al., 2019). The pupillary light response is believed to provide insight into the interworking of both cranial nerve functions and potential intracranial pathologies (Lussier, Stutzman, et al., 2019).

Another aspect of the neurological examination is the state of consciousness, which is usually assessed from the Glasgow Coma Scale (GCS). One study has found that in evaluating TBI patients, mortality increased from 51% to 74% when the patient presented with a lower GCS score, coupled with a worsened pupillary examination. The study aimed to show that in creating a more complete visualization of the patients with TBI, we as health care providers can be more astute to the need for treatment or increased vigilance in a possibly changing examination (Brennan et al., 2018). In addition, a similar study comparing adult and pediatric TBI outcomes found that although pediatric outcomes were more favorable than adult outcomes for severe TBI and poor GCS exams, the pupillary response examination was most telling. If pupils were either fixed on examination or dilated bilaterally, there was a higher mortality rate (Emami et al., 2017).

Although the pupillary response should be considered when evaluating a TBI patient because it may provide insight into treatment needs, there is a shift to predicting status change in patients or the ability to provide advanced warning of neurological decline. In one case, serial pupillary response was used in patients to assess for transtentorial herniation secondary to elevated intracranial pressure. In their evaluation, QP data were used, and it was found that in 73% of patients with brain herniation, a pupillary abnormality was noted by the pupillometer (Papangelou et al., 2018). Additional data revealed that these abnormalities were recorded at a median of 7.4 hours before the herniation event. Another study showed a weak relationship between the Neurological Pupil index (NPi) responses and intracranial pressure elevation in TBI patients (Stevens et al., 2019). Based on these two studies, it seems that pupillary assessment data are necessary for adequate examinations in TBI patients and that the data from the pupillometer may assist in predicting when neurological decline may occur in neurosurgical patients, allowing the treating team to have more time to prepare for surgical intervention (Stevens et al., 2019).

Methods

This study used pragmatic sampling to assess PLR in patients with known or suspected TBI. All study procedures were approved by the institutional review board before study initiation. Patients were eligible for this study if they were admitted to the ED with a suspected TBI and received a standard-of-care PLR assessment using the NPi-200 (Neuroptics Inc.) at baseline and again within 24 hours after admission. NPi-200 readings, and abstracted data from the electronic medical record (EMR), were deidentified and added to a database for analysis. Examples of metrics abstracted from the EMR included race, ethnicity, medical history, and disposition at discharge. NPi-200 devices are easy-to-use handheld devices capable of detecting multiple different QP metrics with minimal training necessary to operate the device. As shown by the existing literature, pupillometers are well liked and straightforward in operating (Tran et al., 2022). ED staff, NPs, and PAs were all trained in using these devices because they are the standard of care at the enrolling institution. Advantages of using standardized pupillometer devices (such as the NPi-200) include their ease, accessibility, and accuracy in obtaining QP data. The NPi-200 device does not capture data unless focused on the pupil, holding the device too high or low results in an error message and need to repeat the scan. Participants were not approached for inclusion if both pupils were not accessible for measurement.

Table 1. Predictors of neuroworsening and abnormal pupillary light reflex[a]

	Neuroworsening (GCS[b])		Abnormal NPi[c] ≤3	
	Yes (n = 35)	No (n = 60)	Yes (n = 23)	No (n = 72)
Gender				
Male	25 (71.43%)	46 (76.67%)	18 (78.26%)	53 (73.61%)
Age median (Q1, Q3)	37 (27.5, 55.5)	50 (36.75, 61.25)	38 (28, 53)	50 (31.5, 61.25)
Race				
White	22 (73.33%),	48 (85.71%)	14 (66.67%)	56 (86.15%)
Black	6 (20.00%)	8 (14.29%)	6 (28.57%)	8 (12.31%)
Asian	2 (6.67%)	0	1 (4.76%)	1 (1.54%)
Ethnicity				
Hispanic	9 (30.00%)	21 (37.50%)	6 (28.57%)	24 (36.92%)
Medical history				
Stroke	1 (5.56%)	3 (6.12%)	1 (8.33%)	3 (5.45%)
Subarachnoid hemorrhage	6 (33.33%)	10 (20.00%)	3 (25.00%)	13 (23.21%)
Prior surgery	27 (77.14%)	19 (32.20%)	15 (65.22%)	31 (43.66%)
Medical intervention required				
Mannitol	15 (42.86%)	8 (13.56%)	10 (43.48%)	13 (18.31%)
Sedation[A]	24 (68.57%)	12 (20.34%)	11 (47.83%)	25 (35.21%)
3% Sodium chloride	12 (34.29%)	4 (6.78%)	9 (39.13%)	7 (9.86%)
Antiseizure medication[B]	24 (68.57%)	43 (72.88%)	15 (65.22%)	52 (73.24%),
Other major medication[C]	26 (74.29%)	27 (45.76%)	15 (65.22%)	38 (53.52%)
Focal neuro deficit (%)	33 (94.29%)	32 (53.33%)	23 (100%)	42 (58.33%)
Disposition at discharge				
Home	10 (29.41%)	41 (69.49%)	9 (39.13%)	42 (60.00%)
Rehab[D]	4 (11.76%)	9 (15.25%)	1 (4.35%)	12 (17.14%)
External care facility	8 (23.52%)	4 (6.78%)	4 (17.40%)	8 (11.43%)
Deceased	12 (35.29%)	1 (1.69%)	9 (39.13%)	4 (5.71%)
Lost to follow-up	0	4 (6.78%)	0	4 (5.71%)

[a]Missing and not reported (e.g., race not given) values are not included.
[b]Glasgow Coma Scale.
[c]Neurological Pupil Index.

QP metrics included the following: neurological pupil index (NPi), pupil latency, diameter, percent change, and relative constriction/dilation velocities. Neuroworsening was defined as a decrease of GCS score of ≥2 points or if the GCS score remained <8 points during the first 24 hours after ED arrival. In addition, instead of considering both QP measurements (left eye and right eye), the lower of the two NPi values was selected. Because an NPi of <3 represents an abnormal PLR response (Giamarino et al., 2021), the resulting NPi measurement was discretized to a binary variable, which was one if the minimum unilateral NPi was <3 and zero otherwise. A chi-square test was performed to test for the association between these two variables.

Statistical analysis

The measures of central tendency were computed and then examined for each baseline received from patients

participating in the study. The primary outcome was a neurological deterioration, derived as ≥ 2-point drop in GCS score from baseline or documented new focal neurological deficit. QP data were dichotomized as normal (NPi >3.0) versus abnormal (NPi ≤ 3.0). The primary hypothesis is analyzed using the chi-square method. All analyses were performed in R (version 4.1.3). Data were available for 99 participants. Of the 99 participants, GCS total data were available for n 96 participants. In addition, one subject did not have NPiL or NPiR measurements available. Therefore, the total number of patients available for analysis was n = 95.

Results

A total of 95 patients were included in the analysis for this study; of which, 25.3% were female, 65.1% were non-Hispanic, and 81.4% were White (**Table 1**). Twenty-three participants had an initial NPi of <3. A total of 35 participants experienced neuroworsening as measured by the GCS at baseline and then again within 24 hours of admission. Of the 35 participants who experienced neuroworsening, 18 had an initial NPi of ≤3. Of the 60 participants who did not experience neuroworsening, five participants had an initial NPi ≤ 3. These results show a significant association between NPi of ≤3 and neuroworsening ($p < .0001$). Although the association between neuroworsening and NPi of ≤3 is statistically significant, the sensitivity of the NPi of ≤3 to predict neuroworsening in our sample is low (51.4%) while having a high specificity (91.7%).

Discussion

The data from this research shows that an abnormal NPi (≤3) at the time of admission for TBI is predictive of neuroworsening within the first 24 hours of admission. This extends our previous knowledge of NPi, which showed that abnormal NPi upon admission for TBI was predictive of an adverse patient outcome (Riker et al., 2020). The results also extend the recent findings of El Ahmadieh et al. (2021) and Kamal et al. (2022), who report that an abnormal NPi finding using QP has high specificity for surgical decision making.

Consistent with prior findings, our data show low sensitivity. This makes intuitive sense because of the many factors related to a patient's outcome after TBI. For example, variances in TBI outcomes have been linked to age, comorbidities, injury severity, time to ED arrival, emergency medical technician intervention, and hospital resources (Iaccarino et al., 2018). In addition, patients presenting with intracranial abnormalities often receive lifesaving medications and treatments that improve their conditions and therefore affect the NPi (Khellaf et al., 2019). These variables were not considered in this study. High specificity is expected as those who do not present with an intracranial trauma would not be expected to have changes to the NPi (Bower et al., 2021).

New technology, treatment options, and assessments continue to be studied for patients with TBI, and as these options become more available, research is needed to better understand treatment options, courses, and the short-term and long-term impact on the patient and clinicians. For NPs often on the front line in assessing these patients, having the most updated technology is paramount for clinical decision making.

Limitations

This is a pilot study to explore the predictability of NPi values for neurological deterioration. This single-center trial started during the pandemic of 2020, which has affected enrollment and data collection. As a tool, GCS is widely used to assess neurological worsening, but it is affected by other factors like consumption of alcohol and drugs and by the intubation status of TBI patients. Another limitation is that GCS does not account for brain stem reflexes. We did not collect data from other scoring systems found in the literature; those in corroboration with GCS can be done in future studies. In addition, more variables (e.g., time of injury, additional demographic information, change in mental status, medical history, and mechanism of injury) could be collected to create a more robust study (Mundluru et al., 2021). We also did not collect data from patients discharged from the hospital within 24 hours, therefore missing many minor contusions.

Conclusion

These data add to the growing body of the literature showing the usefulness of the pupillometer and PLR changes as indicated by the pupillometer. Specifically, the data from this study showed predictive values of unhealthy NPi and patient neurological status at 24 hours post hospitalization. However, further research with a larger sample size is warranted to better understand the lower sensitivity levels. In addition, other pupillometry parameters (latency and constriction velocity) can be assessed to further tease out the relationship with GCS.

Authors' contributions: *T. Trent was the principal investigator of this study. She developed the hypothesis and protocol. In addition, she collected patient data and developed the manuscript. A. Vashisht was the research coordinator of this study. She submitted the study to the institutional review board, collected patient data, and assisted in manuscript development. S. Stutzman was the coinvestigator of this study. She assisted in protocol and manuscript development. D.M. Olson was the faculty sponsor of this study. He provided mentorship and guidance in the hypothesis, protocol, and manuscript development. He collected patient data and assisted in*

manuscript development. He collected patient data and assisted in manuscript development. M. McCreary was personnel for this study. He completed all statistics for this study and assisted in manuscript development.

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