Automated Pupillometry as a Triage and Assessment Tool in Patients with Traumatic Brain Injury

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■ OBJECTIVE: Traumatic brain injury (TBI) is a leading cause of morbidity and mortality in young adults. Automated infrared pupillometry (AIP) has shown promising results in predicting neural damage in aneurysmal subarachnoid hemorrhage and ischemic stroke. We aimed to explore potential uses of AIP in triaging patients with TBI. We hypothesized that a brain injury severe enough to require an intervention would show Neurologic Pupil Index (NPI) changes.

■ METHODS: We conducted a prospective pilot study at a level-1 trauma center between November 2019 and February 2020. AIP readings of consecutive patients seen in the emergency department with blunt TBI and abnormal imaging findings on computed tomography were recorded by the assessing neurosurgery resident. The relationship between NPI and surgical intervention was studied.

■ RESULTS: Thirty-six patients were enrolled, 9 of whom received an intervention. NPI was dichotomized into normal (≥3) versus abnormal (<3) and was predictive of intervention (Fisher exact test; P < 0.0001). Six of the 9 patients had a Glasgow Coma Scale (GCS) score ≤8 and imaging signs of increased intracranial pressure (ICP) and underwent craniectomy (n = 4) or ICP monitor placement (n = 2) and had an abnormal NPI. Three patients

underwent ICP monitor placement for GCS score ≤8 in accordance with TBI guidelines despite minimal imaging findings and had a normal NPI. The GCS score of these patients improved within 24 hours, requiring ICP monitor removal. NPI was normal in all patients who did not require intervention.

■ CONCLUSIONS: AIP could be useful in triaging comatose patients after blunt TBI. An NPI ≥3 may be reassuring in patients with no signs of mass effect or increased ICP.

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of mortality and disability in young adults and affects more than 60 million people every year worldwide.[1,2] After early resuscitation, the initial management of patients with severe TBI revolves around a thorough yet precise neurologic assessment primarily reflected by the Glasgow Coma Scale (GCS) score, and an evaluation of the extent of injuries shown on admission computed tomography (CT).[3-5] This assessment constitutes the basis of evidence on which the Brain Trauma Foundation guidelines are written.6 However, current recommendations only serve as an adjunct to clinical judgment, especially in scenarios in which the evidence is uncertain, because care is often complex and needs

to be tailored to the individual needs of the injured.[3,6] Moreover, these guidelines apply only after transport to treatment centers, do not address patient triage on the field or in transit, and may lead to overuse of surgical resources. The evaluation of the pupillary light reflex (PLR) using automated infrared pupillometry (AIP) has been recently established as a useful source of clinical data in the management of an array of neurologic diseases.[7-10] This evaluation includes the assessment of early brain herniation in ischemic stroke,[11] the correlation with intracranial pressure (ICP) in patients with TBI,[12] and the prediction of cerebral ischemia after aneurysmal subarachnoid hemorrhage.[13] AIP changes also serve as a biomarker following cardiac arrest and extracorporeal membrane oxygenation.[12,14]

The objective of this study was to explore potential uses of AIP in the triage of patients with TBI. We hypothesized that patients with severe head trauma requiring an emergent intervention, including emergent surgical decompression and intracranial monitor or ventricular drain placement, would have changes in their pupillometry readings that could provide insight into their pattern and severity of injury. We aimed to explore the possibility of using this information as an adjunct to GCS and clinical examination to identify severely injured patients requiring emergent surgical treatment early and to prioritize their transfer to capable centers of care.

METHODS

Study Population

This was a prospective observational pilot study conducted at a level 1 trauma center between November 2019 and February 2020. The AIP readings of consecutive patients who presented with a blunt TBI and abnormal imaging findings on CT in the emergency department were recorded by the assessing neurosurgery resident. Neurosurgery is consulted for every TBI with abnormal findings on brain imaging per our trauma protocol. The AIP readings were collected only once and for each side. The assessment was made during the initial neurosurgical examination in the emergency department when the patient was first seen by the resident. Patients with penetrating brain trauma were excluded, because our aim was to study closed injuries after blunt trauma. Patients who had damage to their ocular globe or severe damage to their orbit compromising vision were also excluded to avoid peripheral causes of pupillary reflex malfunction. The AIP readings were obtained using a NeurOptics NPI-200 device (NeurOptics, Laguna Hills, California, USA). The staff neurosurgeon in charge made all decisions of patient care, including emergent interventions. The study protocol was approved by our institutional review board (IRB number STU072017-046).

Data Collection

Data were collected prospectively and included patient demographics, admission GCS score, size and reactivity of the pupils, information regarding the type and velocity of the trauma and the type of treatment administered, and pupillometer readings. Complete AIP readings were stored electronically and sent to the research team. CT findings on admission were also recorded and independently verified by the lead investigator. The modified

Rankin Scale (mRS) score was determined at 3 months for all patients.

Neurological Pupil Index

The significance of the Neurological Pupil Index (NPI) has been previously described in detail.[9,10,13,15,16] Pupillometers use infrared technology to assess several pupillary variables including initial pupil size, pupillary response latency, constriction velocity, smallest pupil size at constriction, and relaxation velocity. These variables are then normalized and standardized to compute the NPI for each eye. The NPI ranges from 0 to 5 and is considered normal for values ≥3. The NPI is believed to reflect direct injury to the oculomotor and visual pathways or indirect damage to cortical, subcortical, or even spinal structures that modulate them.[17-20] For analysis purposes, the NPI score was dichotomized into normal (≥3) and abnormal (<3). The lowest NPI value from each pair of recordings (either from the left or the right eye) was used in our statistical analysis because it would reflect the worse injury to the patient, although the readings for both eyes are presented in **Tables 1** and **2**.

Statistical Analysis

Data were imported from the electronic medical record and the pupillometer data bank to an Excel spreadsheet and subsequently entered into SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) for analysis. Parametric and nonparametric measures of central tendency were derived for baseline and demographic data and to support the assumption of normal distribution. Continuous data are expressed as mean and standard deviation (SD); nominal data are expressed as frequency and percent. Univariate analyses were performed with analysis of variance for continuous variables and a Fisher exact test was used for dichotomous variables with a predetermined α level of significance of 0.05.

RESULTS

A total of 36 patients were enrolled in the study, with 27 (75%) males and a mean age of 49.9 years (SD = 18.9) (**Table 1**). Fifty percent of patients (n = 18) had a high impact velocity injury, which included motor vehicle collisions (n = 14) and falls from a height (n = 4). The other half (n = 18) had low impact velocity injuries, which included falls from standing (n = 13) and assaults (n = 5). A total of 9 patients received emergent neurosurgical procedures on arrival and comprised the emergent intervention group. The other 27 patients did not receive any emergent neurosurgical intervention and comprised the noninterventional group. Neurosurgical interventions included emergent surgical craniectomies in 4 patients, intraparenchymal monitor placements in 4 patients, and external ventricular drain (EVD) placement in 1 patient (**Table 2**).

When comparing the interventional and noninterventional groups, there was no significant difference in patient age (P = 0.1580), gender (P = 0.2665), type of trauma (P = 0.0681), injury velocity (P = 0.0543), or difference in baseline pupil size (P = 0.65 [left eye]; P = 0.43 [right eye]). There was a statistically significant difference in the admission GCS score (P < 0.0001), the admission NPI (P < 0.0001), the pupillary constriction

Table 1. Univariate Comparisons of Emergent Intervention Group versus Noninterventional Group			
	Noninterventional Group (n = 27)	**Emergent Intervention Group (n = 9)**	**P Value**
Age (years)	52.56 (19.94)	42.22 (13.31)	0.1580
Sex, n (% group)			0.2665
Female	8 (29.6)	1 (11.1)	
Male	19 (70.4)	8 (88.9)	
Glasgow Coma Scale Score, mean/median (SD)	13.85/14 (2.3)	6.56/7 (2.13)	<0.0001
Injury velocity, n (% group)			0.0543
Low	16 (59.3)	2 (22.2)	
High	11 (40.7)	7 (77.8)	
Trauma type (% group)			0.0681
Assault	3 (11.1)	2 (22.2)	
Fall from standing	13 (48.2)	0	
High fall	2 (7.4)	2 (22.2)	
Motor vehicle collision	9 (33.3)	5 (55.6)	
Neurological Pupil Index			
Left eye	4.36 (0.38)	3.09 (1.74)	0.0009
Right eye	4.35 (0.36)	3.10 (1.46)	<0.0001
Lowest (left or right)	4.24 (0.40)	2.74 (1.30)	<0.0001
Pupil size			
Left eye	3.69 (0.98)	3.48 (1.61)	0.6451
Right eye	3.75 (1.06)	3.37 (1.54)	0.4292
Constriction velocity (mm/second)			
Left eye	2.04 (0.88)	0.87 (0.66)	0.0017
Right eye	2.10 (1.03)	0.82 (0.63)	0.0026
Dilation velocity (mm/second)			
Left eye	0.95 (0.50)	0.31 (0.23)	0.0014
Right eye	0.81 (0.42)	0.30 (0.26)	0.0054
Values are mean (standard deviation) except where indicated otherwise.			

velocity (P < 0.01), and the dilatation velocity (P < 0.01) (Table 1). The NPI score was significantly lower for the intervention versus noninterventional group (mean, 4.24, SD, 0.4 vs. mean, 2.7, SD, 1.3, respectively; P < 0.0001). None of the patients in the noninterventional group had NPI values <3, and the NPI dichotomized as normal (≥3) versus abnormal (<3) was a predictor of intervention (Fisher exact test, P < 0.0001). The higher NPI scores were associated with better outcome, as shown by lower mRS scores at 3 months (r2 = 0.383; P < 0.0001). The eye with the abnormal NPI was on the side of worse injury, especially in patients who underwent surgical decompression (Table 2).

All patients who underwent an emergent surgical intervention had low GCS scores of ≤8 on admission (Table 2). Six patients in that group had CT scan findings independently warranting an emergent intervention: patients 3, 4, 5, and 8 had extra-axial hematomas with severe brain compression and midline shift and underwent a surgical decompression. Patient 1 had severe bifrontal contusions causing mass effect and received an intraparenchymal bolt-type monitor placement. Patient 9 had severe diffuse brain edema and underwent an EVD placement. Both patients 1 and 9 had ICP that was consistently increased and required aggressive osmolar medical treatment to maintain <20 mm Hg. The NPI was abnormally low (<3) in all these patients on admission.

Patients 2, 6, and 7 had minimal traumatic subarachnoid hemorrhage on their CT scan with signs of diffuse axonal injury and no indicators of imminent herniation. However, these patients underwent an intraparenchymal ICP monitor placement because of a GCS score ≤8 and associated factors in accordance with the TBI guidelines (level IIB). The NPI of these patients was normal (≥3) bilaterally on admission. ICP remained normal with no increases and the monitor was discontinued in all 3. There were 2 patients in the noninterventional group whose GCS was <8 and who met the criteria for ICP monitor placement according to the TBI guidelines (Figure 1); however, the decision to defer placement was made by the attending neurosurgeon. The GCS score of these patients improved to >8 in >24 hours. When our results were assessed by GCS score severity, 11 patients had a severe TBI with a GCS score <8 at presentation. Nine of those patients underwent an invasive procedure (Table 2). Four patients underwent a craniectomy, and 5 patients underwent the placement of an ICP monitor. The NPI was <3 in the patients who underwent an open decompression and in patients 1 and 9.

Three patients died (mRS score 6 at 3 months) in this series, all of whom belonged to the intervention group. Only 1 patient in the intervention group was under the influence of alcohol (patient 1). The effect of alcohol, recreational drugs, and rapid-sequence intubation on AIP values is being studied elsewhere and was not the focus of this study (Table 2).
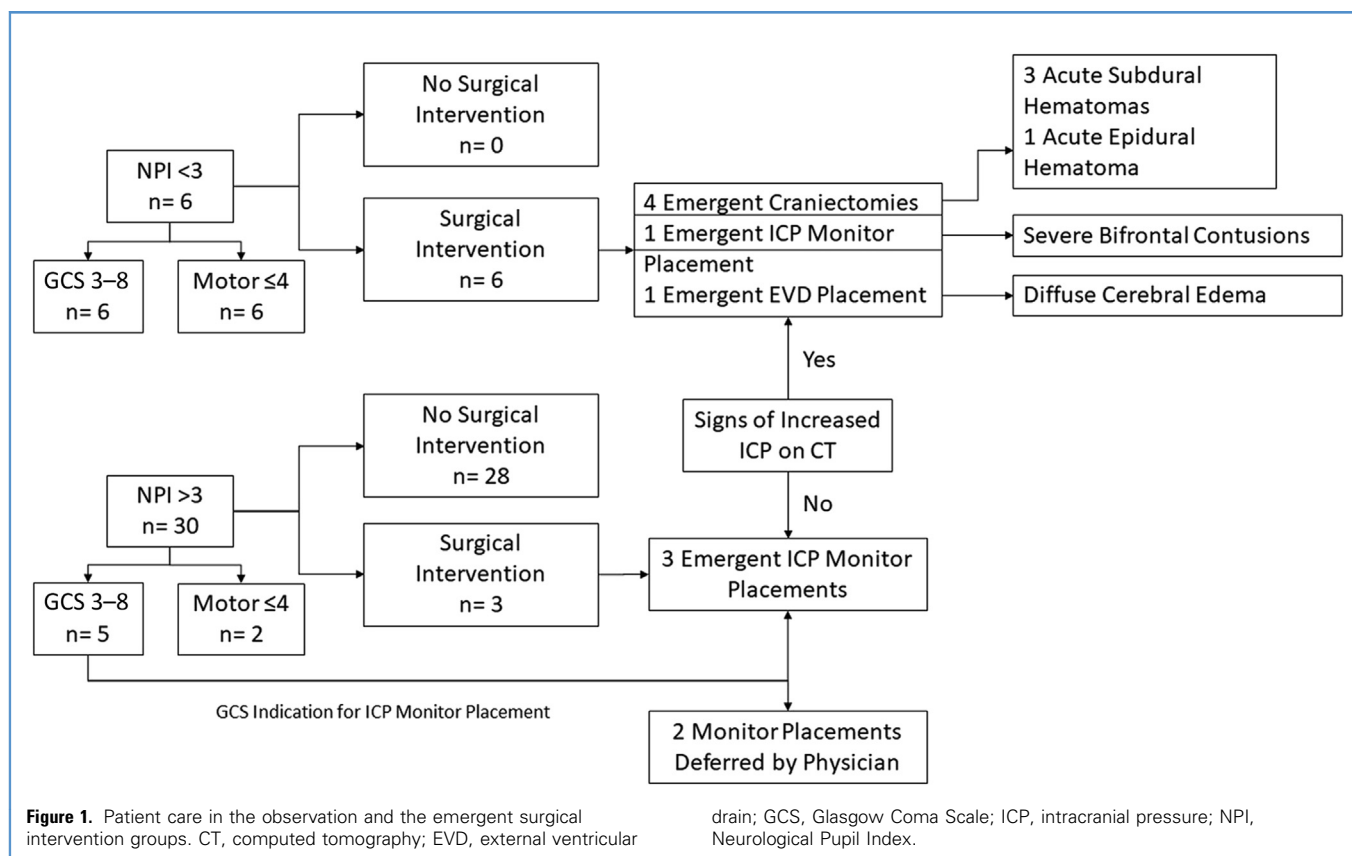
DISCUSSION

Pupillary reactivity depends on intact efferent and afferent visual motor pathways but is also influenced by spinal parasympathetic signals and cortical modulation.[17-20] These pathways can be disrupted by traumatic injury and induce changes registered by the pupillometer. The importance of the pupillary reflex in the assessment of patients with TBI is highlighted by the fact that the GCS-Pupil[4,21] and the Full Outline of Unresponsiveness scale[22,23] both include PLR assessment. However, the GCS-Pupil and the Full Outline of Unresponsiveness scale rely on subjective assessment of the pupil scored as either unreactive or reactive. Subjective PLR assessment can be unreliable and although an unreactive pupil can be a late sign of injury,[24,25] PLR abnormalities before the finding of dilated and nonreactive pupils may provide support to decision making and patient prognostication.[26,27]

Results from our pilot population show that the NPI is significantly lower in patients who undergo emergent procedures for TBI (Table 1). The emergent intervention group consisted of 9

Table 2. Table Detailing the Injury Profile, Intervention, and Outcomes of Patients in the Emergent Intervention Group

Patient Number (Age, years)	Causal Injury	Glasgow Coma Scale Score on Arrival/Motor Score	Intoxicated (Alcohol/ Drugs)	Fixed Dilated Pupils on Clinical Examination	Admission Neurological Pupil Index		Computed Tomography Findings (Marshall Score)	Emergent Intervention	Result of Intervention	Modified Rankin Scale Score at 3 Months
					R Eye	L Eye				
1 (35)	MVC	6/4	Yes	No	1.9	4.8	Severe bifrontal (R>>L) contusions (III)	ICP monitor placement	Severe ICP increases requiring medical treatment	2
2 (45)	MVC	7/5	No	No	4	3.9	Diffuse subarachnoid hemorrhage DAI (II)	ICP monitor placement	Low ICP. removed monitor in 24 hours	4
3 (49)	MVC	6/4	No	No	2.5	4.6	Large R epidural hematoma (VI)	Craniectomy	Decrease in ICP	3
4 (48)	High fall	8/4	No	No	2.9	0.6	Large L subdural hematoma (VI)	Craniectomy	Decrease in ICP	6
5 (32)	High fall	6/4	No	No	2.8	3.2	Large R epidural hematoma (VI)	Craniectomy	Decrease in ICP	0
6 (71)	Assault	6/4	No	No	4.4	4.4	Frontal contusion DAI (II)	ICP monitor placement	Low ICP. Removed monitor in 24 hours	3
7 (39)	Assault	6/4	No	No	4	3.8	DAI (II)	ICP monitor placement	Low ICP. Removed monitor in 24 hours	6
8 (36)	MVC	6/4	No	No	4.6	2.5	Large L subdural hematoma (VI)	Craniectomy	Decrease in ICP	5
9 (25)	MVC	3/1	No	Yes	0	0	Diffuse brain edema DAI (III)	External ventricular drain placement	Severe ICP increases requiring medical treatment	6

R, right; L, left; MVC, motor vehicle collision; ICP, intracranial pressure; DAI, diffuse axonal injury.

Figure 1. Patient care in the observation and the emergent surgical intervention groups. CT, computed tomography; EVD, external ventricular drain; GCS, Glasgow Coma Scale; ICP, intracranial pressure; NPI, Neurological Pupil Index.

patients, all of whom had a GCS score ≤8. Only 6 of these patients had CT findings that would warrant surgical intervention, and 3 underwent ICP monitor/EVD placement to comply with TBI guidelines but had no signs of herniation, mass effect, or diffuse cerebral edema on imaging. The NPI of these 3 patients remained normal. These findings confirm previously reported data showcasing that AIP measurements can potentially serve as an indicator of structural or ischemic injury to the brain.[13,15,28,29] These data suggest that pupillometry readings such as the NPI could be useful as an additional parameter to consider when evaluating patients with a GCS score ≤8 and a mildly abnormal CT scan with no evidence of increased ICP, diffuse brain edema, or mass effect. Although TBI guidelines recommend the placement of an ICP monitor in this subcategory of patients, neurosurgeons may be reluctant to perform invasive procedures in patients whose imaging findings suggest that ICP is likely normal.[30,31] This was the case in 2 patients in our series who did not undergo ICP monitor placement despite qualifying for one based on the guidelines and who had an improvement in their GCS score within 24 hours of admission. Although we recognize the usefulness of the guidelines set by the Brain Trauma Foundation, AIP may provide additional point that could influence clinical and surgical decisions, which warrants future investigation.

The primary hypothesis of this study was that automated pupillometry may provide insight into the pattern of injury of

patients with TBI and may serve as an adjunct to CT in the hospital setting or as an instrument for the triage of unconscious patients and as a red flag for a severe brain injury. Our data suggest that an abnormal NPI (<3) in a comatose patient with a GCS score ≤8 can be an early indicator of pupillary reflex pathway compromise that could require an intervention. This intervention could consist of the emergent placement of an ICP monitor for ICP-guided medical treatment or a craniotomy/craniectomy to decompress a space-occupying lesion and reduce increased ICP. Determining which intervention is needed (craniotomy vs. placement of a parenchymal monitor) still requires a CT scan but incentivizes paramedics and workers to hasten the transfer of the patient to a center with neurosurgical capabilities. The examination of a comatose patient can be rendered difficult by the presence of alcoholic or narcotic intoxication, and because many patients are intubated emergently for airway protection using rapid-sequence paralytics that deprive the examiner from performing a meaningful clinical examination, it can be difficult to assess their injury without a CT scan. The presence of abnormally low NPI could serve as a signal that would prompt first responders to prioritize the transfer of such patients to adequate centers of care. The same scenario could apply to the battlefield by providing medics with an easy way of triaging unresponsive injured soldiers and transporting those with neurosurgical emergencies back to their field hospital promptly. A portable device could also facilitate

care in low-resource environments on a global level. Although a fixed and dilated pupil can predict unilateral or bilateral cerebral injury, this finding is typically delayed and often present in the advent of irreversible or lasting injury. Only 1 patient in our cohort had that finding and subsequently died of his injury (Table 2). All other patients in the intervention group had reactive pupils bilaterally. Anisocoria in a patient with bilaterally reactive pupils may carry some prognostic value, but that was not the subject of this study. The lowest NPI that was abnormal seemed to belong to the eye on the side of the worst injury, specifically in patients who underwent surgical decompression (Table 2).

Determining the true value of automated pupillometry as an aid in surgical decision making in severe TBI requires studies with larger groups of patients admitted with a GCS score <8 and will likely have to involve several trauma centers. Automated pupillometry may also have a role to play in gauging the impact of minor head trauma such as concussion, but that determination was beyond the scope of the current study.

Limitations

Some limitations to this study should be acknowledged. First, this is early work and constitutes a feasibility pilot investigative study. Our sample size is small and with heterogenous causes of injury. Second, although only 1 patient in our emergent procedure group was intoxicated, the effects of alcohol or drug consumption on pupillary reactivity and AIP readings still need to be explored and may have influenced our readings. Although every effort was made to include all neurosurgical consults with blunt trauma in this study, it is possible that some cases were inadvertently missed, which may bias our results.

CONCLUSIONS

AIP may be useful in the initial triage of comatose patients after blunt TBI. A low NPI may be indicative of severe brain injury requiring an emergent surgical procedure. Pupillometry readings may provide additional data that can be helpful in the management of comatose patients with a GCS score ≤8 when their brain imaging does not show direct signs of herniation, midline shift, or increased ICP.

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